F 0/32 - /38 H 8/458033

NOVEL COMPOUNDS

1/3

This invention relates to certain substituted thiazolidinedione derivatives, to a process for preparing such compounds, to pharmaceutical compositions containing such compounds and to the use of such compounds and compositions in medicine.

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Blint

9 European Patent Applications, Publication Numbers
10 0008203, 0139421, 0155845, 0177353, 0193256, 0207581 and
11 0208420 relate to thiazolidinedione derivatives which are
12 disclosed as having hypoglycaemic and hypolipidaemic
13 activity. Chem. Pharm. Bull 30 (10) 3580-3600 also
14 relates to certain thiazolidinedione derivatives having
15 hypoglycaemic and hypolipidaemic activities.

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17 It has now surprisingly been discovered that certain 18 novel substituted-thiazolidinedione derivatives show 19 improved blood-glucose lowering activity and are 20 therefore of potential use in the treatment and/or 21 prophylaxis of hyperglycaemia and are of particular use 22 in the treatment of Type II diabetes. These compounds 23 are also indicated to be of potential use for the 24 treatment and/or prophylaxis of other diseases including 25 hyperlipidaemia and hypertension.

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27 They are also indicated to be of use in the treatment 28 and/or prophylaxis of cardiovascular disease, especially 29 atherosclerosis. In addition these compounds are 30 considered to be useful for treating certain eating 31 disorders, in particular the regulation of appetite and 32 food intake in subjects suffering from disorders 33 associated with under-eating , such as anorexia nervosa, and disorders associated with over-eating, such as 34 35 obesity and anorexia bulimia.

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37 Accordingly, the present invention provides a compound of 38 formula (I):

or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein:

 ${\bf A}^{\bf l}$ represents a substituted or unsubstituted aromatic heterocyclyl group;

Rl represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group, wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group;

 \mathbb{R}^2 and \mathbb{R}^3 each represent hydrogen, or \mathbb{R}^2 and \mathbb{R}^3 together represent a bond;

 ${\tt A}^2$ represents a benzene ring having in total up to five substituents; and

n represents an integer in the range of from 2 to 6.

Suitable aromatic heterocyclyl groups include substituted or unsubstituted, single or fused ring aromatic heterocyclyl groups comprising up to 4 hetero atoms in each ring selected from oxygen, sulphur or nitrogen.

Favoured aromatic heterocyclyl groups include substituted or unsubstituted single ring aromatic heterocyclyl groups having 4 to 7 ring atoms, preferably 5 or 6 ring atoms.

In particular, the aromatic heterocyclyl group comprises 1, 2 or 3 heteroatoms, especially 1 or 2, selected from oxygen, sulphur or nitrogen.

01	- 3 -
02	Suitable values for A ¹ when it represents a 5- membered
0 3	aromatic heterocyclyl group include thiazolyl and
04	oxazolyl, especially oxazolyl.
05	
06	Suitable values for A ¹ when it represents a 6- membered
07	aromatic heterocyclyl group include pyridyl or
08	pyrimidinyl.
09	
10	Suitably R^2 and R^3 each represent hydrogen.
11	
12	Preferably, A^1 represents a moiety of formula (a), (b)
13	or (c):
14	R^4
15	R4
16	R^{5}
17	R R S
18	(a) (b) (c)
19	
20	wherein:
21	${ t R}^4$ and ${ t R}^5$ each independently represents a hydrogen
22	atom, an alkyl group or a substituted or unsubstituted
23	aryl group or when R^4 and R^5 are each attached to
24	adjacent carbon atoms, then R^4 and R^5 together with the
25	carbon atoms to which they are attached form a benzene
26	ring wherein each carbon atom represented by R^4 and R^5
27	together may be substituted or unsubstituted; and in
28	the moiety of formula (a)
29	X represents oxygen or sulphur.
30	13 ···
31	Aptly, A ¹ represents a moiety of the abovedefined
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Aptly, A^{1} represents a moiety of the abovedefined

formula (a).

formula (b).

01 02	$^-$ 4 $^-$ Aptly, ${\sf A}^1$ represents a moiety of the abovedefined
0 3	formula (c).
04	
05	In one favoured aspect \mathbb{R}^4 and \mathbb{R}^5 together represent a
06	moiety of formula (d):
07	• ,
08	
09	-6
10	R ⁶
11	*/ -
12	(d)
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14	wherein R^6 and R^7 each independently represent
15	hydrogen, halogen, substituted or unsubstituted alkyl
16	or alkoxy.
17	
18	Suitably, R^6 and R^7 each independently represent
19	hydrogen, halogen, alkyl or alkoxy.
20	- -
21	Favourably, R ⁶ represents hydrogen. Favourably,
22	R ⁷ represents hydrogen.
23	
24	Preferably, R^6 and R^7 both represent hydrogen.
25	
26	In a further favoured aspect \mathbb{R}^4 and \mathbb{R}^5 each
27	independently represent hydrogen, alkyl or a
28	substituted or unsubstituted phenyl group and more
29	favourably, R^4 and R^5 each independently represent
30	hydrogen, alkyl or phenyl.
31	
32	Preferably, for the moiety of formula (a), R^4 and R^5
33	together represent the moiety of formula (d).
34	
35	Preferably, for the moieties of formula (b) or (c), R^4
36	and R ⁵ both represent hydrogen.

It will be appreciated that the five substituents of A^2 include three optional substituents. Suitable optional substituents for the moiety A^2 include halogen, substituted or unsubstituted alkyl or alkoxy.

Favourably, A^2 represents a moiety of formula (e):

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wherein R^8 and R^9 each independently represent ...ydrogen, halogen, ___stituted or unsubstituted alkyl or alkoxy.

Suitably, R^8 and R^9 each independently represent hydrogen, halogen, alkyl or alkoxy. Preferably, R^8 and R^9 each represent hydrogen.

Favourably, X represents oxygen. Favourably, X represents sulphur.

In one preferred aspect the present invention provides a class of compounds, which fall wholly within the scope of formula (I), of formula (II):

$$A^{1} - H - (CH_{2}) - O + CH_{2} + C$$

or a tautomeric form thereof, and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, wherein A^1 , R^1 , R^2 , R^3 , and n are as defined in relation to formula (I) and R^8 and R^9 are as defined in relation to formula (e).

Surtably, n represents an integer 2, 3 or 4, notably 2 or 3 and especially 2.

Suitably, R^1 represents hydrogen, alkyl, acyl, especially acetyl, or benzyl.

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when \mathbb{R}^1 represents an alkyl group, examples of such alkyl groups include methyl and isopropyl. Preferably, \mathbb{R}^1 represents a methyl group.

As indicated above a compound of formula (I) may exist in one of several tautomeric forms, all of which are encompassed by the present invention. It will be appreciated that the present invention encompasses all of the isomeric forms of the compounds of formula (I) and the pharmaceutically acceptable salts thereof, including any stereoisomeric forms thereof, whether as individual isomers or as mixtures of isomers.

Suitable substituents for any heterocyclyl group include up to 4 substituents selected from the group consisting of: alkyl, alkoxy, aryl and halogen or any two substituents on adjacent carbon atoms, together with the carbon atoms to which they are attached, may form an aryl group, preferably a benzene ring, and wherein the carbon atoms of the aryl group represented by the said two substituents may themselves be substituted or unsubstituted.

When used herein the term 'aryl' includes phenyl and naphthyl optionally substituted with up to five, preferably up to three, groups selected from halogen, alkyl, phenyl, alkoxy, haloalkyl, hydroxy, amino, nitro, carboxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonyloxy, or alkylcarbonyl groups.

When used herein the term 'halogen' refers to fluorine, chlorine, bromine and iodine; preferably chlorine.

when used nerein the terms 'alkyl' and 'alkoxy' relate to groups having straight or branched carbon chains, containing up to 12 carbon atoms.

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When used herein the term 'acyl' includes alkylcarbonyl groups.

Suitable alkyl groups are C_{1-12} alkyl groups, especially C_{1-6} alkyl groups e.g. methyl, ethyl, n-propyl, iso-propyl, n-butyl, isobutyl or tert-butyl groups.

Suitable substituents for any alkyl group include those indicated above in relation to the term ''aryl''.

Suitable pharmaceutically acceptable salts include salts of the thiazolidinedione moiety, and, where appropriate, salts of carboxy groups.

Suitable pharmaceutically acceptable salts of the thiazolidinedione moiety include metal salts especially alkali metal salts such as the lithium, sodium and potassium salts.

Suitable pharmaceutically acceptable salts of carboxy groups include metal salts, such as for example aluminium, alkali metal salts such as sodium or potassium, alkaline earth metal salts such as calcium or magnesium and ammonium or substituted ammonium salts, for example those with lower alkylamines such as triethylamine, hydroxy alkylamines such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)-amine or tri-(2-hydroxyethyl)-amine, cycloalkylamines such as bicyclohexylamine, or with procaine, dibenzylpiperidine, N-benzyl- β -phenethylamine, dehydroabietylamine, N,N'-bisdehydroabietylamine, glucamine, N-methylglucamine or bases of the pyridine type such as pyridine, collidine or quinoline.

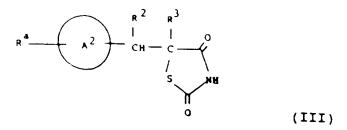
Surtable pharmaceutically acceptable solvates include hydrates.

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 In a further aspect the present invention also provides a process for the preparation of a compound of formula (I), or a tautomeric form thereof, and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, which process comprises reacting a compound of formula (III):



wherein \mathbb{R}^2 , \mathbb{R}^3 and \mathbb{A}^2 are as defined in relation to formula (I), and \mathbb{R}^a is a moiety convertible to a moiety of formula (f):

$$\begin{vmatrix}
R^{1} \\
A^{1}-N-(CH_{2})_{n}-O
\end{vmatrix}$$
 (f)

wherein R¹, A¹, and n are as defined in relation to formula (I), with an appropriate reagent capable of converting R^a to the said moiety (f) and thereafter, if required, carrying outrone or more of the following optional steps:

- (i) converting a compound of formula (I) to a further compound of formula (I);
- (ii) preparing a pharmaceutically acceptable salt of the compound of formula (I) and/or a pharmaceutically acceptable solvate thereof.

Suitably, R^a represents $R^1HN^-(CH_2)_{\Pi}^-O$ -wherein R^1 and Π are as defined in relation to formula (I).

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Suitably, when R^a is $R^1HN-(CH_2)_n-O-$, an appropriate reagent capable of converting R^a to a moiety (f) is a compound of formula (IV):

$$A^1 - R^X$$
 (IV)

wherein A^1 is as defined in relation to formula (I) and $R^{\mathbf{X}}$ represents a leaving group.

A suitable leaving group $R^{\mathbf{X}}$ includes a halogen atom, preferably a chlorine or bromine atom, or a thioalkyl group for example a thiomethyl group.

The reaction between the compound of formula (III) and the appropriate reagent may be carried out under conditions suitable to the particular compound of formula (III) and the reagent chosen; thus for example the abovementioned reaction between a compound of formula (III) wherein R^a represents $R^1HN-(CH_2)_n-O-$ and the compound of formula (IV), may be carried out in any suitable solvent, for example tetrahydrofuran, at a temperature in the range of between 0 and 60°C.

A compound of formula (III) may be prepared from a compound of formula (V):

$$R^b$$
 CHO (V)

wherein A^2 is as defined in relation to the compound of formula (I) and R^b is a moiety R^a , or a moiety convertible to a moiety R^a ; by reaction of the compound of formula (V) with 2,4-thiazolidinedione; and

01 - 10 thereafter if required carrying out one or more of the 02 03 following optional steps: 04 reducing a compound of formula (III) wherein \mathbb{R}^2 05 and \mathbb{R}^3 together represent a bond, into a compound of 06 formula (III) wherein \mathbb{R}^2 and \mathbb{R}^3 each represent 07 08 hydrogen; 09 converting a moiety R^{b} to a moiety R^{a} . 10 (ii)11 The reaction between the compound of formula (V) and 12 2,4-thiazolidinedione will of course be carried out 13 under conditions suitable to the nature of the compound 14 of formula (V), in general the reaction being carried 15 16 out in a solvent such as toluene, suitably at an elevated temperature such as the reflux temperature of 17 18 the solvent and preferably in the presence of a suitable catalyst such as piperidinium acetate or 19 benzoate. Favourably, in the reaction between the 20 compound of formula (V) and 2,4-thiazolidinedione, the 21 22 water produced in the reaction is removed from the reaction mixture, for example by means of a Dean and 23 24 Stark apparatus. 25 When R^a represents $R^1HN-(CH_2)_{\Pi}-O-$, a suitable value for 26 Rb is a hydroxyl group. 27 28 The moiety $R^{\mathbf{b}}$ may be converted to the moiety $R^{\mathbf{a}}$ by any 29 suitable means, for example when Rb represents a 30 hydroxyl group and R^a represents $R^1HN(CH_2)_n$ -O- the 31 appropriate conversion may be carried out by coupling a 32

compound of formula (VA):

0 1 0 2	- 11 -	
0 3	2 3	
04	R R O	
05	$\begin{pmatrix} A^2 \end{pmatrix}$ CH $\begin{pmatrix} C \end{pmatrix}$	Z
06	\searrow \downarrow $\stackrel{!}{\stackrel{!}{\stackrel{!}{\stackrel{!}{\stackrel{!}{\stackrel{!}{\stackrel{!}{\stackrel{!}$	
07	но /	
08		(VA)
09		,
10	wherein R^2 , R^3 and A^2 are as defined in r	elation to
11	formula (I) and R^Z is hydrogen or a nitro	
12	group, with a compound of formula (VI):	
13		
14	R ¹ NRX(CH ₂) ₂ =OH	. /117 \

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 $R^{\perp}NR^{\wedge}(CH_2)_{n}-OH$ (VI)

wherein R^{l} and n are as defined in relation to formula (I) and $R^{\mathbf{X}}$ is hydrogen or a nitrogen protecting group, in the presence of a suitable coupling agent; and thereafter, if required, carrying out one or more of the following optional steps:

- reducing a compound of formula (III) wherein \mathbb{R}^2 and \mathbb{R}^3 together represent a bond, to a compound of formula (III) wherein \mathbb{R}^2 and \mathbb{R}^3 each represent hydrogen;
- (ii) removing any nitrogen protecting group.

A suitable coupling agent for the coupling reaction between the compound of formula (VA) and (VI) is provided by diethylazodicarboxylate and triphenylphosphine. The coupling reaction may be carried out in any suitable solvent at a low to medium temperature, for example in tetrahydrofuran at a temperature in the range of between 0 and 60°C.

One example of the preparation of a compound of formula (VA) is that wherein a compound falling within formula

01 (V) of particular formula (VII): 02 0.3 04 05 06 07 08 (VII) 09 wherein A^2 is as defined in relation to formula (I), 10 and R¹¹ represents a hydroxyl group or a protected 11 hydroxyl group, is reacted with 2,4-thiazolidinedione; 12 and thereafter if required removing any protecting 13 14 group. 15 Preferably, R11 represents a benzyloxy group. 16 17 Suitable conditions for the reaction between a compound 18 of formula (VII) and 2,4-thiazolidinedione are those 19 defined above in relation to the reaction between the 20 compounds of formula (V) and 2,4-thiazolidinedione. 21 22 The compounds of formula (IV), (VI) and (VII) are 23 either known compounds or are prepared using methods 24 analogous to those used to prepare known compounds. 26 Suitable protecting groups in any of the abovementioned 27 reactions are those used conventionally in the art. 28 29 Thus, for example, a suitable nitrogen protecting group is a benzyl group or a benzyloxycarbonyl group and a 30 suitable hydroxyl protecting group is a benzyl group. 31 32 The methods of formation and removal of such protecting 33 34 groups are those conventional methods appropriate to 35 the molecule being protected. Thus for example when R11 represents a benzyloxy group such group may be 36

prepared by treatment of the appropriate compound of

formula (VII), wherein R ¹¹ is a hydroxyl group with a benzyl halide, such as benzyl bromide, and thereafter when required the benzyl group may be conveniently removed using a mild ether cleavage reagent such as trimethylsilyliodide. A compound of formula (I), or a tautomeric form thereof, and/or a pharmaceutically acceptable salt
when required the benzyl group may be conveniently removed using a mild ether cleavage reagent such as trimethylsilyliodide. A compound of formula (I), or a tautomeric form
removed using a mild ether cleavage reagent such as trimethylsilyliodide. A compound of formula (I), or a tautomeric form
06 trimethylsilyliodide. 07 08 A compound of formula (I), or a tautomeric form
07 08 A compound of formula (I), or a tautomeric form
A compound of formula (I), or a tautomeric form
to the state of th
thereof, and/or a pharmaceutically acceptable salt
thereof and/or a pharmaceutically acceptable solvate
thereof, may also be prepared by reacting a compound of
12 formula (VIII):
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14 R
15
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$
$A^2 - N - (CH_2) = 0$
18 (VIII)
19
wherein R^1 , A^1 , A^2 , and n are as defined in relation to
formula (I) with 2,4-thiazolidinedione; and thereafter
if required carrying out one or more of the following
optional steps:
24 (i) converting a compound of formula (I) into a
further compound of formula (I);
26 (ii) preparing a pharmaceutically acceptable salt of
a compound of formula (I) and/or a pharmaceutically
28 acceptable solvate thereof.
29
The reaction between a compound of formula (VIII) and
31 2,4-thiazolidinedione may suitably be carried out under
analogous conditions to those used in the reaction
between a compound of formula (V) and
34 2,4-thiazolidinedione.
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A compound of formula (VIII) may be prepared by

reacting a compound of formula (IX):

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 A^2

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(IX)

wherein A^2 is as defined in relation to formula (I) and R^a is as defined in relation to formula (III), with an appropriate reagent capable of converting R^a to the above defined moiety (f).

Suitable values for R^a include those described above in relation to the compound of formula (III). Thus R^a may represent $R^1HN-(CH_2)_n-O-$, as defined above, and hence the appropriate compound of formula (IX) may be reacted with a reagent of the abovedefined formula (IV) to provide the required compound of formula (VIII).

Suitable reaction conditions for the reaction of the compound of formula (IX) and the appropriate reagent may include those described above in relation to the preparation of compound (III) with the said appropriate reagent.

Preferably, for the compound of formula (IX), R^a represents a leaving group, especially a fluorine atom. When R^a represents a leaving group, preferably a fluorine atom, a particularly appropriate reagent is a compound of formula (X):

$$R^{1}$$

$$\downarrow$$
 $A^{1}-N-(CH_{2})_{n}-OH$
(X)

wherein $\mathbf{R}^{\mathbf{l}}$, $\mathbf{A}^{\mathbf{l}}$, and n are as defined in relation to 02 formula (I). 0.3 04 The reaction between the compounds of formulae (IX) and 05 (X) may be carried out under any suitable conditions, 06 for example in a solvent such as dimethylformamide or 07 dimethylsulphoxide at an elevated temperature for 0.8 example in the range of between 100 to 150°C, suitably 09 in the presence of a base such as sodium hydride or 10 11 potassium carbonate. 12 13 In the compound of formula (IX) R^a may also represent a 14 hydroxyl group. 15 When R^{a} , in the compound of formula (IX), represents a 16 hydroxyl group a particularly appropriate reagent is a 17 compound of the above defined formula (X) or a compound 18 19 of formula (XA): 20 R^1 $A^1-N-(CH_2)_{\Omega}-ORY$ 21 22 23 24 wherein $\mathbf{A}^{\mathbf{l}}$, $\mathbf{R}^{\mathbf{l}}$ and n are as defined in relation to 25 formula (X) and RY represents a tosylate or mesylate 26 2**7** group. 28 29 The reaction between the compound of formula (IX) wherein Ra is a hydroxyl group and the reagent of the 30 31 abovedefined formula (X) may suitably be carried out in 32 an aprotic solvent, such as tetrahydrofuran, at low to medium temperature, for example at ambient temperature, 3.3 and preferably in the presence of a coupling agent such 34 as that provided by triphenylphosphine and 35

diethylazodicarboxylate.

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(XA)

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The reaction between the compound of formula (IX), wherein R^a is a hydroxyl group, and the reagent of the abovedefined formula (XA) may be carried out in an aprotic solvent, such as dimethylformamide, at a low to elevated temperature, for example in the range of from 50°C to 120°C and preferably in the presence of a base, such as sodium hydride.

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The compound of formula (XA) may be prepared from the corresponding compound of formula (X) by reaction with either a tosyl halide or a mesyl halide in a solvent such as pyridine.

The compounds of formula (IX) are known compounds or compounds prepared by methods analogous to those used to prepare known compounds, for example 4-fluorobenzaldehyde and 4-hydroxybenzaldehyde are known commercially available compounds.

The reagent of formula (X) may be prepared by reacting a compound of the hereinabove defined formula (IV), with a compound of the hereinbefore defined formula (VI) and thereafter if required removing any nitrogen protecting group using the appropriate conventional conditions.

The reaction between the compounds of formula (IV) and (VI) may be carried out under any suitable conditions, such as in solvent, for example in an aprotic solvent such as tetrahydrofuran, at a low to medium temperature, for example a temperature in the range of from 0 to 60° C.

Favourably when \mathbb{R}^1 represents hydrogen the reaction is carried out using the compound of formula (VI) as a solvent at a low to elevated temperature, suitably an

01 elevated temperature such as in the range of between 02 03 100 and 170°C. 04 The abovementioned conversion of a compound of formula 05 (I) into a further compound of formula (I) includes the 06 07 following conversions: 08 09 reducing a compound of formula (I) wherein \mathbb{R}^2 and \mathbb{R}^3 together represent a bond, to a compound of 10 formula (I) wherein \mathbb{R}^2 and \mathbb{R}^3 each represent hydrogen; 11 12 13 converting one group R^1 into another group R^1 . 14 (b) 15 The conversion of a compound of formula (I) to a 16 further compound of formula (I) may be carried out by 17 18 using any appropriate conventional procedure. 19 20 A suitable reduction method for the abovementioned conversion (a) includes catalytic reduction or the use 21 22 of a metal/solvent reducing system. 23 Suitable catalysts for use in the catalytic reduction 24 are palladium on carbon catalysts, preferably a 10% 25 26 palladium on charcoal catalyst; the reduction being carried out in a solvent, for example dioxan, suitably 27 28 at ambient temperature. 29 30 Suitable metal/solvent reducing systems include 31 magnesium in methanol. 32 33 The abovementioned reduction of a compound of formula (III) wherein ${\ensuremath{\mathsf{R}}}^2$ and ${\ensuremath{\mathsf{R}}}^3$ together represent a bond to a 34 35 compound of formula (III) wherein R^2 and R^3 each 36 represent hydrogen, may be carried out under analogous

conditions to those referred to above in conversion (a) of the compound of formula (I).

In the abovementioned conversion (b), suitable conversions of one group \mathbb{R}^1 into another group \mathbb{R}^1 includes converting a group \mathbb{R}^1 which represents hydrogen into a group \mathbb{R}^1 which represents an acyl group.

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The conversion of a compound of formula (I) wherein \mathbb{R}^1 represents hydrogen into a compound of formula (I) wherein \mathbb{R}^1 represents acyl may be carried out using any appropriate conventional acylation procedure, such as by treating an appropriately protected compound of formula (I) with an acylating agent. For example acetic anhydride may be used to prepare the compound of formula (I) wherein \mathbb{R}^1 is acetyl.

It will be appreciated that in the abovementioned conversions (a) and (b), any reactive group in the compound of formula (I) would be protected, according to conventional chemical practice, where necessary.

Where appropriate the isomeric forms of the compounds of formula (I) and the pharmaceutically acceptable salts thereof may be prepared as individual isomers using conventional chemical procedures.

As mentioned above the compounds of the invention are indicated as having useful therapeutic properties:

The present invention accordingly provides a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use as an active therapeutic substance.

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1 2 Thus the present invention provides a compound of formula 3 (I), or a tautomeric form thereof and/or a 4 pharmaceutically acceptable salt thereof and/or a 5 pharmaceutically acceptable solvate thereof, for use in 6 the treatment of and/or prophylaxis of hyperglycaemia, 7 hyperlipidaemia and hypertension. 8 9 A compound of formula (I), or a tautomeric form thereof 10 and/or a pharmaceutically acceptable salt thereof and/or 11 a pharmaceutically acceptable solvate thereof, may be 12 administered per se or, preferably, as a pharmaceutical 13 14 composition also comprising a pharmaceutically acceptable 15 carrier. 16 17 Accordingly, the present invention also provides a pharmaceutical composition comprising a compound of the 18 19 general formula (I), or a tautomeric form thereof, or a pharmaceutically acceptable salt thereof, or a 20 pharmaceutically acceptable solvate thereof, and a 21 pharmaceutically acceptable carrier therefor. 22 23 As used herein the term 'pharmaceutically acceptable' 24 embraces compounds, compositions and ingredients for both 25 human and veterinary use: for example the term 26 27 'pharmaceutically acceptable salt' embraces a veterinarily acceptable salt. 28 29 The composition may, if desired, be in the form of a pack 30 accompanied by written or printed instructions for use. 31 32 Usually the pharmaceutical compositions of the present 33 34 invention will be adapted for oral administration, although compositions for administration by other routes, 35

such as by injection and percutaneous absorption are also

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envisaged.



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3 Particularly suitable compositions for oral

4 administration are unit dosage forms such as tablets and

5 capsules. Other fixed unit dosage forms, such as powders

6 presented in sachets, may also be used.

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8 In accordance with conventional pharmaceutical practice

9 the carrier may comprise a diluent, filler, disintegrant,

10 wetting agent, lubricant, colourant, flavourant or other

11 conventional adjuvant.

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13 Typical carriers include, for example, microcrystalline

14 cellulose, starch, sodium starch glycollate,

15 polyvinylpyrrolidone, polyvinylpolypyrrolidone, magnesium

16 stearate, sodium lauryl sulphate or sucrose.

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18 Most suitably the composition will be formulated in unit

19 dose form. Such unit dose will normally contain an

20 amount of the active ingredient in the range of from 0.1

21 to 1000 mg, more usually 0.1 to 500 mg, and more

22 especially 0.1 to 250 mg.

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24 The present invention further provides a method for the

25 treatment and/or prophylaxis of hyperglycaemia or

26 hyperlipidaemia in a human or non-human mammal which

27 comprises administering an effective, non-toxic, amount

28 of a compound of the general formula (I), or a tautomeric

29 form thereof and/or a pharmaceutically acceptable salt

30 thereof and/or a pharmaceutically acceptable solvate

31 thereof to a hyperglycaemic human or non-human mammal in

32 need thereof.

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35 The present invention further provides a method for the

36 treatment of cardiovascular disease, especially

37 atherosclerosis, in a human or non-human mammal, which

38 comprises administering an effective, non-toxic, amount

39 of a compound of formula (I), or a tautomeric form



thereof and/or a pharmaceutically acceptable salt thereof 1 2 and/or a pharmaceutically acceptable solvate thereof, to 3 a human or non-human mammal in need thereof.

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5 The present invention also provides a method for the 6 treatment of certain eating disorders, in particular the 7 regulation of appetite and food intake in disorders 8 associated with under-eating, such as anorexia nervosa, 9 and disorders associated with over-eating, such as 10 obesity and anorexia bulimia, in a human or non-human 11 mammal, which comprises administering an effective, 12 non-toxic, amount of a compound of formula (I), or a 13 tautomeric form thereof and/or a pharmaceutically 14 acceptable salt thereof and/or a pharmaceutically 15 acceptable solvate thereof, to a human or non-human

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mammal in need thereof.

Conveniently, the active ingredient may be administered as a pharmaceutical composition hereinbefore defined, and this forms a particular aspect of the present invention.

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22 In the above mentioned treatments the compound of the 23 general formula (I), or a tautomeric form thereof and/or 24 a pharmaceutically acceptable salt thereof and/or a 25 pharmaceutically acceptable solvate thereof, may be taken 26 in doses, such as those described above, one to six times 27 a day in a manner such that the total daily dose for a 70 28 kg adult will generally be in the range of from 0.1 to 29 6000 mg, and more usually about 1 to 1500 mg.

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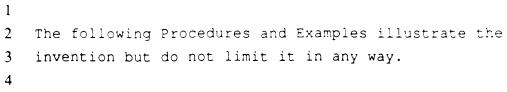
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In the treatment and/or prophylaxis of hyperglycaemic non-human mammals, especially dogs, the active ingredient may be adminstered by mouth, usually once or twice a day and in an amount in the range of from about 0.025 mg/kg to 25 mg/kg, for example 0.1 mg/kg to 20 mg/kg. dosage regimens are suitable for the treatment and/or prophylaxis of hyperlipidaemia in non-human mammals.

- 22 -



01 02	- 23 - Preparation 1
03	reparteron 1
04	4-[2-/N-Methyl N /2 hopgothiagalyl) tackathawa
05	4-[2-(N-Methyl-N-(2-benzothiazolyl)amino)ethoxy]- benzaldehyde
06	<u>Delizaldenyde</u>
-	
07	
08	N CH_ CHO
09	N CH 3
	s
11	
12	
13	
14 .	A mixture of 4-fluorobenzaldehyde (1.5g) and 2-
15	[N-methyl-N-(2-benzothiazolyl)amino]ethanol (2.4g) in
16	dimethyl sulphoxide (50ml) containing anhydrous
17	potassium carbonate (2g) was stirred at 100°C for 24
18	hours. The mixture was cooled to room temperature and
19	added to water (300ml). The aqueous solution was
20	extracted with diethyl ether (2x300ml). The organic
21	extracts were washed with brine (1x300ml), dried
2 2	(MgSO ₄), filtered and evaporated to dryness. The title
23	compound was obtained as a waxy solid following
24	chromatography on silica-gel in 1% methanol in
25	dichloromethane.
26	
27	1H NMR δ (CDC13)
28	
29	3.2 (3H, s); 3.8 (2H, t); 4.2 (2H, t);

6.8-7.8 (8H, complex); 9.8 (1H, s).

			24	
Pr <u>eparat</u> ion	2			

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2-[N-Methyl-N-(2-benzothiazolyl)amino]ethanol

C

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A mixture of 2-chlorobenzothiazole (8.5g) and 2-methylaminoethanol (20ml) was heated at 120°C under pressure in a sealed, glass lined, stainless steel reaction vessel for 18 hours. After cooling, the oil was added to water (100ml), extracted with dichloromethane (2x100ml), the organic extracts were dried (MgSO₄), filtered and evaporated to dryness. Chromatography of the residual oil on silica-gel in 21/2% methanol in dichloromethane gave the title compound which was used in Preparation 1 without further purification.

1H NMR & (CDCl3)

3.15 (3H, s); 3.4-4.0 (4H, m); 4.7 (1H, broad s, exchanges with D_2O); 6.8-7.6 (4H, complex).

Preparation 3

3 20 3

04 <u>4-[2-(N-Methy</u> 05 benzaldehyde

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80

09 10

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13 14

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2 **3**

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2**7** 2**8**

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3**4** 3**5**

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4-[2-(N-Methyl-N-(2-benzoxazolyl)amino)ethoxy]-benzaldehyde

To a solution of 2-[N-methyl-N-(2-benzoxazolyl) amino]ethanol (9.6g), triphenylphosphine (13.1g) and 4-hydroxybenzaldehyde (6.1g) in dry tetrahydrofuran (150ml) was added dropwise a solution of diethyl azodicarboxylate (9.0g) in dry tetrahydrofuran (30ml), under a blanket of nitrogen with stirring at room temperature. The solution was stirred overnight at room temperature following which the solvent was removed under reduced pressure. The residue was dissolved in diethyl ether (300ml), filtered and the ether solution was washed with dilute sodium hydroxide solution (200 ml), saturated brine (200ml), dried (MgSO₄), filtered and the solvent evaporated. The title compound (mp 97-98°C) was obtained after chromatography on silica-gel, eluting with dichloromethane.

1H NMR δ (CDCl₃)

3.30 (3H, s); 3.85 (2H, t); 4.30 (2H, t) 6.80-7.85 (8H, complex); 9.85 (1H, s).

02 <u>Preparation 4</u>

 2-[N-Methyl-N-(2-benzoxazolyl)amino]ethanol

OF OF

A solution of 2-chlorobenzoxazole (15.4g) in dry tetrahydrofuran (50ml) was added dropwise to an ice cooled solution of 2-methylaminoethanol (15.0g) in dry tetrahydrofuran (100ml) with stirring and protection from atmospheric moisture. The mixture was stirred at 0°C for 1 hour, allowed to warm to room temperature and stirred for a further 2 hours. The solvent was removed under reduced pressure, the product was dissolved in ethyl acetate (200ml) and washed with brine (2x150ml). The organic layer was dried (MgSO₄), filtered and the solvent evaporated. Chromatography of the residue on silica-gel in dichloromethane gave the title compound (mp 62-3°C) which was used in Preparation 3 without further purification.

1H NMR δ (CDCl3)

3.12 (3H s); 3.4-4.0 (4H, m); 4.7 (1H, s, exchanges with D_2O); 6.8-7.4 (4H, complex).



01 - 27 -02 Preparation 5 0.3 4-[2-(N-Methyl-N-(2-pyrimidinyl)amino)ethoxy]-04 05 benzaldehyde 06 27 3 C 09 10 11 12 13 14 15 A mixture of 4-fluorobenzaldehyde (12ml) and 2-[N-methyl-N-(2-pyrimidinyl)amino]ethanol (10.05g) in 16 dry dimethyl sulphoxide (50ml) containing anhydrous 17 potassium carbonate (15g) was stirred at 120°C for 6 18 hours. The mixture was cooled to room temperature and 19 added to water (200ml). The aqueous solution was 20 extracted with ethyl acetate (2 x 300ml), the organic 21 22 extracts washed with brine, dried (MgSO $_4$) and evaporated. The title compound was obtained as an oil 23 following chromatography on silica-gel in 2% methanol 24 in dichloromethane. 25 26 27 1H NMR δ (CDCl₃)

> 3.3 (3H, s); 3.8-4.4 (4H, complex); 6.5 (1H, t); 7.0 (2H, d); 7.8 (2H, d); 8.3 (2H, d); 9.9 (1H, s).

28 29

- 28 -Preparation 6 2-[N-Methyl-N-(2-pyrimidinyl)amino]ethanol A mixture of 2-chloropyrimidine (10g) and 2-methylaminoethanol in dry tetrahydrofuran (100ml) was boiled under reflux for 3 hours. The solution was cooled, water (200ml) was added, the mixture extracted with dichloromethane, the organic extracts were dried (MgSO₄), filtered and evaporated to dryness. The residual oil was used in Preparation 5 without further

1H NMR δ (CDCl₃)

purification.

4 5

3.2 (3H, s); 3.5-3.9 (4H, m); 4.6 (1H, s, exchanges with D_2O); 6.4 (1H, t); 8.2 (2H, d).

Preparation 7

2-[N-Methyl-N-(2-[4,5-dimethylthiazolyl])amino]ethanol

- 29 -

4 5

CH₃ N CH₃

CH₃ S OH

A solution of 2-chloro-4,5-dimethylthiazole (13.2g) and 2-methylaminoethanol (40ml) in pyridine (100ml) was boiled under reflux for 20 hours. After cooling, the oil was added to water (300ml) and extracted with ethyl acetate (3x200ml). The organic extracts were washed with brine (2x200ml), dried (MgSO₄), filtered and evaporated to dryness to leave the title compound which was used in Preparation 14 without further purification.

1H NMR δ (CDCl₃)

2.15 (3H, s); 2.20 (3H, s); 3.1 (3H, s); 3.4-3.9 (4H, m); 5.25 (1H, broad s, exchanges with D_2O).

01 02	- 30 - Preparation 8
03	respondent o
04	2-[N-Methyl-N-(2-thiazolyl)amino]ethanol
05	
06	
07	
08	
09	$ \begin{array}{c c} & & \\$
10	OH OH
11	\$
12	
13	
14	
15	The title compound was prepared as an oil from
16	2-bromothiazole (15g) and 2-methylaminoethanol (45ml)
17	by an analogous procedure to that described in
18	Preparation 7
19	
20	1H NMR δ (CDCl ₃)
21	
22	3.1 (3H, s); 3.4-3.9 (4H, m); 4.8 (1H, broad s,
23	exchanges with D ₂ O); 6.4 (1H, d); 7.0 (1H, d).
24	
25	Preparation 9
26	
27	2-[N-Methyl-N-(2-(4-phenylthiazolyl))amino]ethanol
28	
29	
30	
31	N CH_
32	N Cn3
33	OH OH
34	Č
35	
36	
37	
38	

- 31 -The title compound was prepared as an oil from 2-chloro-4-phenylthiazole (13.5g) and 2-methylaminoethanol (40ml) by an analogous procedure to that described in Preparation 7. 1H NMR δ (CDCl₃) 3.15 (3H, s); 3.6-4.0 (4H, m); 4.6 (1H, broad s, exchanges with D_2O); 6.7 (1H, s); 7.2-7.9 (5H, complex). Preparation 10 2-[N-Methyl-N-(2-(4-phenyl-5-methylthiazolyl))amino] ethanol The title compound was prepared as an oil from **9** 2-chloro-4-phenyl-5-methylthiazole (18.9g) and 2-methylaminoethanol (50ml) by an analogous procedure to that described in Preparation 7. **3** 1H NMR δ (CDCl₃) 2.38 (3H, s); 3.0 (3H, s); 3.45-3.85 (4H, m); 5.1 (1H,

broad s, exchanges with D_2O); 7.1-7.7 (5H, complex).

01	- 32 -
02	Preparation 11
03	
04	2-[N-Methyl-N-(2-(4-methyl-5-phenylthiazolyl))amino]-
05 、	<u>ethanol</u>
06	
07	
08	
09	CH ₃ N CH ₋
10	$_{\text{CH}_3}$ $_{\text{N}}$ $_{\text{CH}_3}$
11	S OH
12	
13	
14	
15	
16	
17	
18	
19	
20	The title compound was prepared as an oil from
21	2-chloro-4-methyl-5-phenylthiazole (14.8g) and
22	2-methylaminoethanol (40ml) by an analogous procedure
23	to that described in Preparation 7.

2.35 (3H, s); 3.1 (3H, s); 3.5-4.0 (4H, m);

5.1 (1H, broad s, exchanges with D_2O);

1H NMR & (CDCl3)

7.1-7.5 (5H, complex).

- 33 -Preparation 12 2-[N-Methyl-N-(2-(4-methylthiazolyl))amino]ethanol The title compound was prepared, by an analogous procedure to that described in Preparation 7, and was used in the next stage without further purification. 1H NMR δ (CDCl₃) 2.25 (3H, s); 3.1 (3H, s); 3.55-3.95 (4H, m); 4.9 (1H, broad s, exchanges with D_2O); 6.1 (1H, s). Preparation 13 2-[N-Methyl-N-[2-(5-phenyloxazolyl)]amino]ethanol

01	- 34 -
02	A solution of 2-chloro-5-phenyloxazole (8.3g) and
03	2-methylaminoethanol (30ml) was stirred at 50°C for 10
04	minutes. After cooling the oil was added to water
05	(250ml) and extracted with ethyl acetate (2x150ml).
06	The organic extracts were washed with brine (2x100ml),
07	dried (MgSO ₄), filtered and evaporated to dryness to
08	leave the title compound (m.p. 73-75°C).
09	
10	1H NMR δ (CDCl ₃)
11	
12	3.2 (3H, s); 3.6 (2H, t); 3.85 (2H, t); 3.9
13	(1H, broad s, exchanges with D_2O); 7.0 (1H, s);
14	7.2-7.55 (5H, complex).
15	
16	Preparation 14
17	
18	4-[2-(N-Methyl-N-(2-(4,5-dimethylthiazolyl)amino)
19	ethoxy) benzaldehyde
20	
21	
22	
2 3	СНО
24	$^{\text{CH}}_{3}$ $^{\text{CH}}_{3}$
25	N 0
26	CH ₃
27	-
28	

31

32

33

34 35 The title compound was prepared from 2-[N-methyl-N-(2-(4,5-dimethylthiazolyl)) amino]ethanol (13.2g) and 4-fluorobenzaldehyde (23.1g) by an analogous procedure to that described in Preparation 5.

01 02	- 35 - 1H NMR & (CDCl3)
03	
04	2.15 (3H, s); 2.2 (3H, s); 3.18 (3H, s); 3.8 (2H, t);
05	4.3 (2H, t); 7.0 (2H, d); 7.8 (2H, d); 10.0 (1H, s).
06	
07	Preparation 15
08	
09	4-[2-(N-Methyl-N-(2-thiazolyl)amino)ethoxy]benzaldehyde
10	
11	
12	
13	
14	CHO CHO
15	N CH 3
16	s
17	
18	
19	
20	
21	The title compound was prepared from 2-[N-methyl-N-
22	(2-thiazolyl)amino]ethanol (10.7g) and 4-fluoro-
23	benzaldehyde (15.9g) by an analogous procedure to that
24	described in Preparation 5.
25	1
26	1H NMR δ (CDCl ₃)
27	2.15 (27) - 2.2 (27) - 1.2 (27) - 1.2 (27) - 1.2 (27) - 2.2
28	3.15 (3H, s); 3.9 (2H, t); 4.4 (2H, t); 6.5 (1H, d);
29	7.0 (2H, d); 7.15 (1H, d); 7.8 (2H, d); 9.9 (1H, s).
30	

01	- 36 -
02	Preparation 16
03	
04	4-[2-(N-Methyl-N-(2-(4-phenylthiazolyl)amino)ethoxy)]
05	benzaldehyde
06	
07	
08	
09	СНО
10	N CH ₃
11	N 0
12	S'
13	
14	
15	
16	The title compound was prepared from 2-[N-methyl-N-
17	(2-(4-phenylthiazolyl))amino]ethanol (16.1g) and
18	4-fluorobenzaldehyde (17.4g) by an analogous procedure
19	to that described in Preparation 5.
20	
21	1H NMR δ (CDCl ₃)
22	

6.95-7.9 (9H, complex); 9.9 (1H, s).

3.2 (3H, s); 3.95 (2H, t); 4.3 (2H, t); 6.7 (1H, s);

23

01 02	- 37 - Preparation 17
03	
04	4-[2-(N-Methyl-N-(2-(4-phenyl-5-methylthiazolyl)amino)
05 `	ethoxy) benzaldehyde
06	
07	
08	
09	
10	CHO CHO
11	N
12	CH ₂ S
13	3
14	
15	
16	
17	
18	
19	The title compound was prepared from 2-[N-methyl-N-
20	(2-(4-phenyl-5-methylthiazolyl))aminojethanol (13g) and
21	4-fluorobenzaldehyde (9.8g) by a similar procedure to
22	that described in Preparation 5.
23	
24	1H NMR & (CDC13)
25	
26	2.35 (3H, s); 3.1 (3H, s); 3.8 (2H, t); 4.2 (2H, t);
27	6.85-7.8 (9H, complex); 9.85 (1H, s).

- 38 -Preparation 18 4-[2-(N-Methyl-N-(2-(4-methyl-5-phenyl-thiazolyl)amino) ethoxy) |benzaldehyde CHO 4-methyl-5-phenylthiazolyl))amino]ethanol (13g) and 4-fluorobenzaldehyde (13g) by an analogous procedure to that described in Preparation 5. 1H NMR δ (CDCl₃) 2.36 (3H, s); 3.2 (3H, s); 3.9 (2H, t); 4.35 (2H, t);

7.05 (2H, d); 7.2-7.5 (5H, complex); 7.85 (2H, d);

9.95 (1H, s).

01	- 39 -
02	<u>Preparation 19</u>
03	
04	4-[2-(N-Methyl-N-(2-(4-methylthiazolyl))amino)ethoxy]
05	<u>benzaldehyde</u>
06	
37	
3 C	
09	CHO
10	CH_3 N O CH_3 O
11	
12	~ 3
13	
14	
15	
16	The title compound was prepared from 2-[N-methyl-N-
17	(2-(4-methylthiazolyl))amino]ethanol (12g) and
18	4-fluorobenzaldehyde (14.3g) by an analogous procedure
19	to that described in Preparation 5.
20	
21	1H NMR 4 (CDCl ₃)
22	
23	2.25 (3H, s); 3.2 (3H, s); 3.9(2H, t); 4.3 (2H, t);
24	6.1 (1H, s); 7.05 (2H, d); 7.85 (2H, d); 9.95 (1H, s).

)1	- 40 -
)2	Preparation 20
3	
34	4-[2-(N-Methyl-N-[2-(5-phenyloxazolyl)]amino)ethoxy]
2 5	<u>benzaldehyde</u>
26	
7	
ე8	
၁ 9	N CH ₃ CHO
10	\sim \sim \sim \sim \sim
11	
12	
13	
14	
1 5	
16	
17	The title compound was prepared from
18	2-[N-methyl-N-(2-(5-phenyloxazolyl))amino]ethanol
19	(9.3g) and 4-fluorobenzaldehyde (7.9g) by an analogous
20	procedure to that described in Preparation 5.
21	
2 2	1H_NMR & (CDCl3)
2 3	
24	3.25 (3H, s); 3.85 (2H, t); 4.3 (2H, t); 6.95-7.6 (8H,
25	complex); 7.8 (2H, d); 9.9 (1H, s).

01	- 41 -
02	Preparation 21
03	
04	2-[N-Methyl-N-[2-(4,5-dimethyloxazolyl)]amino]ethanol.
05	
06	
07	
08	24
09	$^{\text{CH}}_{3}$ $^{\text{N}}$ $^{\text{CH}}_{3}$
10	OH OH
11	CH ₃
12	
13	
14	
15	
16	A solution of 2-chloro-4,5-dimethyloxazole (5g) and
17	2-methylaminoethanol (15ml) was stirred at 120°C for 40
18	minutes. After cooling the oil was added to water
19	(200ml) and extracted with dichloromethane (3x200ml).
20	The organic extracts were washed with brine (2x100ml),
21	dried (MgSO $_4$), filtered and evaporated to dryness to
22	leave the title compound as a waxy solid, which was

1H NMR δ (CDCl₃)

2324

2526

27

28 29 used in Preparation 22 without further purification.

1.95 (3H, s); 2.10 (3H, s); 3.05 (3H, s); 3.5 (2H, t);

3.8 (2H, t); 4.4 (1H, broad s, exchanges with D_2O).

01 02	Preparation 22
03	
04	4-[2-(N-Methyl-N-[2-(4,5-dimethyloxazolyl)]amino)
05	ethoxy benzaldehyde
06	
07	
08	
09	$CH_3 \sim N$, $CH_3 \sim CHO$
10	\sim N
11	CH ₃
12	
13	
14	
15	To a stirred solution of 2-[N-methyl-N-[2-(4,5-
16	dimethyloxazolyl)aminojethanol (2.7g) in DMF (60ml),
17	under an atmosphere of nitrogen, was added portionwise
18	sodium hydride (0.7g; 60% dispersion in oil). After
19	the vigorous reaction had subsided, 4-fluoro-
20	benzaldehyde (2.9g) was added and the reaction mixture
21	was heated to 80°C for 16 hours. After cooling, the
2 2	mixture was added to water (400ml). The aqueous
23	solution was extracted with diethyl ether (3x250ml).
24	The organic extracts were washed with brine (2x100ml),
25	dried (MgSO ₄), filtered and evaporated to dryness. The
26	title compound was obtained as an oil following chroma-
27	tography of the residue on silica-gel in 1% methanol in
28	dichloromethane.
29	
30	1H NMR δ (CDCl ₃)
31	
32	1.95 (3H, s); 2.15 (3H, s); 3.15 (3H, s); 3.8 (2H, t);

4.25 (2H, t); 7.0 (2H, d); 7.9 (2H, d); 10.0 (1H, s).

01 02	- 43 - <u>Preparatio</u> n 23
0 3	
04	2-(N-(2-Benzoxazolyl)-N-methylamino)ethanol 4-toluene-
05	sulphonyl ester
06	
07	
08	N, CH,
09	O CH 3 CH 3
10	O ₃ s — CH ₃
11	
12	
13	
14	4-Toluenesulphonyl chloride (19.0g) was added portion-
15	wise to a solution of N-(2-benzoxazolyl)-N-methyl-
16	aminoethanol (19.2g) in dry pyridine (100 ml) at room
17	temperature. The mixture was stirred at room
18	temperature for 3 hours, added to water (500 ml) and
19	extracted with dichloromethane (3x250 ml). The
20	combined extracts were washed with 2M hydrochloric acid
21	(3x250 ml), saturated sodium bicarbonate solution
22	(250 ml) and brine (250 ml), dried (MgSO $_4$), filtered
23	and evaporated. The title compound was obtained pure
24	following crystallisation from ethanol (m.p.
25	119-121°C).
26	4
27	$\frac{1}{H}$ NMR & (DMSO-d ₆)
28	
29	2.25 (3H, s); 3.05 (3H, s); 3.75 (2H, t); 4.35 (2H, t);

7.0 - 7.4 (6H, complex); 7.70 (2H, d).

- 44 -Preparation 24 2-(N-(2-Benzoxazolyl)-N-methylamino)ethanol methane-sulphonyl ester The title compound (m.p. 97-8°C) was prepared from N-(2-benzoxazolyl)-N-methylaminoethanol (19.2g) and methanesulphonyl chloride (11.5g) by a similar procedure to that used in Preparation 23. 1H NMR δ (CDCl₃) 2.90 (3H, s); 3.25 (3H, s); 3.7 (2H, t); 4.5 (2H, t); 6.90 - 7.4 (4H, complex). Preparation 25 4-[2-(N-Methyl-N-(2-benzoxazolyl)amino)ethoxy]benzaldehyde

To a solution of 4-hydroxybenzaldehyde (7.32g) in dry

01 02	- 45 - dimethylformamide (100ml) was added portionwise sodium
03	hydride (60%, 2.4g) with stirring at room temperature
04	under nitrogen. When gas evolution ceased a solution
05	of 2-(N-methyl-N-(2-benzoxazolyl)amino)ethanol
06	4-toluenesulphonyl ester (17.3g) in dry
07	dimethylformamide was added dropwise. The mixture was
08	heated to 80°C and stirred at this temperature
09	overnight. After cooling, the solution was poured into
10	iced water (1 litre), extracted with ethyl acetate
11	(3x500ml), and the combined extracts were washed with
12	sodium hydroxide solution (2M; 500ml) and brine
13	(500ml), dried (MgSO ₄), filtered and evaporated. The
14	title compound (m.p. 96-98°C) was obtained pure after
15	crystallisation from ethanol.
16	
17	1H NMR δ (DMSO-d ₆)
18	
19	3.25 (3H, s); 3.95 (2H, t); 4.40 (2H, t);
20	6.90-7.40 (6H, complex); 7.85 (2H, d); 9.90 (1H, s).
21	
22	Preparation 26
23	
24	4-[2-(N-Methyl-N-(2-benzoxazolyl)amino)ethoxy]-
25	<u>benzaldehyde</u>
26	
27	
28	
29	N CH ₃
30	N N
31	
32	
33	
34 35	
36	

The title compound was prepared from 4-hydroxy

37

)1	- 46 -
)2	benzaldehyde (1.22g) and 2-(N-methyl-N-(2-benzoxazolyl)
)3	-amino)ethanol methanesulphonyl ester (2.7g) in a
04	similar manner to that described in Preparation 25.
05	•
)6	
)7	Preparation 27
)8	
) 9	2-(2-Pyrimidinylamino)ethanol
_ 0	
_1	
. 2	
₋ 3	N .
.4	OH
. 5	N NH OH
. 6	
.7	
.8	
.9	2-Chloropyrimidine (5g) and ethanolamine (15ml) were
20	stirred for 2 hours at 140°C. After cooling, the
21	mixture was added to water (200ml) and continuously
22	extracted with ethyl acetate (500ml) for 16 hours. The
23	organic extract was dried (MgSO ₄), filtered and
24	evaporated to dryness. The title compound was obtained
25	as a solid (m.p. 66°C), following chromatography on
26	silica-gel in 3% methanol in dichloromethane.
27	
28	1H NMR & (CDCl3)
?9	
30	3.55 (2H, complex); 3.8 (2H, t); 4.3 (1H, broad s,

exchanges with D_2O); 6.1 (1H, broad s, exchanges with

D₂O); 6.55 (1H, t); 8.3 (2H, d).

31 32

01 02	- 47 - Preparation 28
03	
04 -	4-[2-(2-Pyrimidinylamino)ethoxy]benzaldehyde
05	
06	
07	
08	N CHO
09	
10	N NH
11	
12	
13	
14	Sodium hydride (1.2g; 60% dispersion in oil) was added
15	portionwise to a stirred solution of 2-(2-pyrimidinyl
16	amino)ethanol (4g) in DMF (140ml) under an atmosphere
17	of nitrogen. After the vigorous reaction had subsided
18	4-fluorobenzaldehyde (5.35g) was added and the solution
19	heated to 80°C for 20 hours. After cooling the mixture
20	was added to water (500ml) and extracted with diethyl
21	ether (3x300ml). The organic extracts were washed with
22	brine ($2x200ml$), dried ($MgSO_4$), filtered and evaporated
23	to dryness. Chromatography of the residue on silica
24	gel in 2% methanol in dichloromethane afforded the
25	title compound, which was used in the next stage
26	without further purification.
27	
28	1H NMR δ (CDCl ₃)
29	

3.8 (2H, complex); 4.2 (2H, t); 5.7 (1H, broad s,

d); 8.3 (2H, d); 9.9 (1H, s).

exchanges with D₂O); 6.5 (1H, t); 7.0 (2H, d); 7.8 (2H,

30

3132

01 02	- 48 - <u>Preparation 29</u>
03	
04	2-(N-(2-Benzothiazolyl)-N-benzylamino)ethanol
05	
06	
07	
08	
၁ 9	
10	
11	S OH
12	
13	
14	
15	2-Chlorobenzothiazole (13g) and 2-(benzylamino)ethanol
16	(29g) were heated together in a sealed vessel at 120°C
17	for 20h After cooling, the reaction mixture was
18	dissolved in ethyl acetate (200ml) and the solution was
19	washed with saturated aqueous sodium hydrogen carbonate
20	(3x100ml), water (3x100ml) and brine (100ml), dried
21	over anhydrous magnesium sulphate and evaporated to
22	give the title compound (m.p. 95-96°C;
23	dichloromethane/hexane).
24	
25	1H NMR 6 (CDCl ₃)
26	
27	3.8 (4H, m); 4.5 (1H, broad s, exchanges with D_2O); 4.7

(2H, s); 6.9-7.7 (9H, complex).

01	- 49 - <u>Preparation</u> 30
03	
04	4-(2-(N-(2-Benzothiazolyl)-N-benzylamino)ethoxy)-
05	benzaldehyde
06	
07	
08	СНО
09	N Sind
10	N N N N N N N N N N N N N N N N N N N
11	S
12	
13	The title compound was prepared from
14	2-(N-(2-benzothiazolyl)-N-benzylamino)ethanol (8.25g)
15	and 4-fluorobenzaldehyde (3.6g) by an analogous
16	procedure to that described in Preparation 22.
17	
18	1H NMR & (CDC13)
19	
20	4.0 (2h, t); 4.4 (2H, t); 4.9 (2H, s); 6.9-8.0 (13H,
21	complex); 10.0 (1H, s).
2 2	
23	Preparation 31
24	
25	4-[3-(N-Methyl-N-(2-benzoxazolyl)-amino)propoxy]benzald
2 6	<u>ehyde</u>
2 7	ava
2 8	СНО
29	N CH ₃
30	
31	0
32	
33	The title compound was prepared from
34	3-[(N-(2-benzoxazolyl)-N-methyl)amino]propan-1-ol
3 5	(7.5g) and 4-fluorobenzaldehyde (6.78g) by a similar

procedure to that described in Preparation 22.

01 02	- 50 - ¹ H NMR δ (CDCl ₃)
03	II MIK 5 (CDC13)
34	2.0-2.4 (2H, complex); 3.2 (3H, s); 3.75 (2H, t); 4.2
25	(2H, t); 6.8-7.5 (6H, complex); 7.8 (2H, d); 9.9 (1H,
26	s).
77	, , , , , , , , , , , , , , , , , , ,
28	Preparation 32
39	
10	3-[(N-(2-Benzoxazolyl)-N-methyl)amino]propan-1-ol
11	
12	
13	
14	N CH 3 OH
15	N OH
16	0'
17	
18	
19	2-Chlorobenzoxazole (15.36g) in dry tetrahydrofuran
2 0	(50ml) was added dropwise to a mixture of
21	3-N-methylaminopropan-1-ol (9.8g) and triethylamine
2 2	(20.2g) in dry tetrahydrofuran (130ml) with stirring,
2 3	at room temperature. After stirring at room
24	temperature overnight the solvent was evaporated. The
2 5	residue was dissolved in dichloromethane (150ml),
26	washed with water (3x100ml), brine (150ml), dried
2 7	(MgSO $_4$), filtered and evaporated. The title compound
28	was obtained as an oil following chromatography on
29	silica-gel in 2.5-3% methanol in dichloromethane.
30	•
31	1H NMR δ (CDCl ₃)
32	
33	1.8-2.1 (2H, complex); 3.2 (3H, s); 3.5-3.85 (4H,

complex); 4.3 (1H, broad s, exchanges with D_2O);

6.8-7.5 (4H, complex).

34 35

Preparation 33 4-[2-(N-Methyl-N-(2-pyridyl)amino)ethoxy]benzaldehyde CH₃ The title compound was prepared from 2-(N-methyl-N-(2-pyridyl)amino)ethanol (8.9g) and 4-fluorobenzaldehyde by a similar procedure to that described in Preparation 22. 1H NMR & (CDCl3) 3.2 (3H, s); 3.8 (2H, t); 4.2 (2H, t); 6.4 (2H, t); 6.9 (2H, d); 7.3 (1H, complex); 7.75 (2H,d); 8.15 (1H,d); 9.9 (1H, s). Preparation 34 4-[N-(2-Benzoxazoyl)-N-methylamino]butan-1-ol **9** 2-Chlorobenzoxazole (15.35g) was added dropwise over 10 minutes to a stirred solution of

1 C - 52 -4-(N-methylamino)butan-1-ol (10.3g) and triethylamine 2 ((20.3g) in dry tetrahydrofuran (150ml). The mixture **3** was stirred at room temperature overnight, and then **)4** heated at reflux for a further 2h. The resulting 25 mixture was cooled and the solvent was evaporated. 26 residue was dissolved in dichloromethane (500ml), **7** washed with saturated sodium bicarbonate solution 38 (3x300ml) and brine (500ml), dried and evaporated to **9** 10 afford the title compound as an oil. 11 12 1H NMR & (CDCl3) 13 1.5-2.0 (4H, complex); 3.1 (3H,s); 3.4-3.9 (5H, 14 complex; reduced to 4H after D_2O exchange); 6.9-7.4 15 16 (4H, complex) 17 18 Preparation 35 19 4-[(N-(2-Benzoxazolyl)-N-methyl)amino]butan-1-ol 20 methanesulphonyl ester 21 22 23 24 25 26 2**7** 28 2**9** Methanesulphonyl chloride (3.15g) was added dropwise to 30 a stirred, ice-cooled solution of 31 32 4-[N-(2-benzoxazolyl)-N-methylamino]butan-1-ol (5.5g) and 4-dimethylaminopyridine (0.15g) in pyridine 3 **3** (100ml). The mixture was allowed to warm to room 34

temperature overnight, and then diluted with water

(500ml), and extracted with dichloromethane (3x200ml).

35

- 53 -The combined extracts were washed with saturated sodium bicarbonate solution (3x200ml), and brine (200ml), then dried and the solvent evaporated to afford an oil. More of this oil was obtained from the acidic aqueous layers by means of adjusting the pH to 4.5 with solid potassium carbonate, re-extracting with dichloromethane (3x200ml), and drying and evaporating these dichloromethane layers. The combined impure product fractions were chromatographed on silica gel with 2% methanol in dichloromethane as eluent to afford the title compound as an oil. 1 H NMR δ (CDCl₃) 1.80(4H,complex); 3.05(3H,s); 3.25(3H,s); 3.60(2H,complex); 4.30(2H,complex); 6.90-7.40(4H, complex). Preparation 36 4-[4-(N-Methyl-N-(2-benzoxazolyl)amino)butoxyl benzaldehyde The title compound was prepared from **3** 4-hydroxybenzaldehyde (1.71g) and 4-[N-(2-benzoxazolyl)-N-methylamino]butan-l-ol methanesulphonyl ester (3.80g) by a similar procedure

to that used in Preparation 26.

01	- 54 - 1H NMR δ (CDCl ₃)
03	
04	1.70-1.95(4H, complex); 3.20(3H,s); 3.55(2H, complex);
05	4.00(2H, complex); 6.80-7.40(6H, complex) 7.75(2H,d);
06	9.90(1H,s)
07	
08	Preparation 37
09	
10	2-[N-(2-Benzoxazolyl)aminojethanol
11	
12	
13	
14	N ₁
15	NH OH
16	
17	
18	
19	A solution of 2-chlorobenzoxazole (12.78g) in dry
20	tetrahydrofuran (50ml) was added, over 10 minutes, to a
21	stirred, ice-cooled solution of ethanolamine (15.3g) in
22	dry tetrahydrofuran (400ml). The mixture was heated at
23	reflux overnight, cooled, and the solvent evaporated.
24	The residue was partitioned between water (500ml) and
25	dichloromethane (500ml), and the resulting white solid
26	filtered off, washed with dichloromethane and dried $\underline{\text{in}}$
27	vacuo to afford the title compound m.p. 162-4°C.
28	
29	1H NMR & DMSO-d6
30	
31	3.3-3.8 (4H, complex); 5.0 (1H, br, exchanges with
32	D_2O); 6.9-7.7 (4H, complex); 8.1 (1H, br, exchanges
33	with D ₂ O).

01	- S5 -
02	Preparation 38
23	
04	2-[N-(2-Benzoxazolyl)amino]ethanol methanesulphonyl
)5	<u>ester</u>
)6	
37	
38	N O ₃ SCH ₃
39	NH O3SCH3
10	0
11	
12	
13	
14	Methanesulphonyl chloride (4.9g) was added dropwise to
15	a stirred, ice-cooled solution of
16	2-[N-(2-benzoxazolyl)amino]ethanol (6.23g) and
17	triethylamine (4.39g) in dichloromethane (75ml). The
18	resulting mixture was stirred at 0°C for 1.5h and then
19	diluted with dichloromethane (200ml), washed with water
20	(2x200ml), brine (200ml) and dried. The
21	dichloromethane layer was evaporated and the residue
2 2	chromatographed on silica gel with 1.5% methanol in
2 3	dichloromethane as eluent to give the title compound,
24	m.p. 96-9°C.
25	
2 6	1H NMR & CDCl3
27	
28	3.0 (3H,s); 3.85 (2H,t); 4.5 (2H,t); 5.9 (1H,br,
2 9	exchanges with D_2O); 7.0-7.5 (4H, complex).
30	

- 56 -Preparation 39 4-[2-(N-(2-Benzoxazolyl)amino)ethoxy]benzaldehyde A mechanically stirred mixture of 2-[N-(2-benzoxazolyl)amino]ethanol methanesulphonyl ester (5.77g), 4-hydroxybenzaldehyde (2.81g) and potassium carbonate (3.28g) was heated at 80°C overnight in dry DMF (250ml). After cooling, the reaction mixture was concentrated <u>in vacuo</u>, diluted with water (500 ml) and extracted with ethyl acetate (3x300ml). The combined ethyl acetate layers were washed with water (2x11), brine (11), dried and evaporated. The resulting solid was chromatographed on silica gel with 1.5% methanol in dichloromethane as eluent to afford the title compound, m.p. 103-6 °C. 1H NMR & CDCla

3.9 (2H,t); 4.3 (2H,t); 6.4 (1H, br, exchanges with

 D_2O); 6.9-8.0 (8H, complex); 9.9 (1H,s).

7 8

01 02	- 57 - Preparation 40
03	
04	2-[N-Isopropyl-N-(2-benzoxazolyl)amino]ethanol
05	
06	
07	,
08	N
09	N N
10	ОН
11	
12	
13	2-Chlorobenzoxazole (23.04g) was added dropwise to an
14	ice-cooled solution of 2-(isopropylamino)ethanol
15	(15.45g) and triethylamine (30.3g) in tetrahydrofuran
16	(500ml). The mixture was stirred at room temperature
17	for 30 minutes, then heated at reflux overnight before
18	being cooled and evaporated. The residue was dissolved
19	in dichloromethane (800ml) and washed with saturated
20	sodium bicarbonate solution (500ml), water (3x11) brine
21	(11), dried (MgSO ₄), filtered and evaporated. The title
22	compound was obtained as an oil following
23	chromatography on silica gel using 1.5%
24	methanol-dichloromethane as solvent.
25	
26	1H NMR & (CDC13)
27	
28	1.25 (6H,d); 3.6 (2H,t); 3.9 (2H,t); 4.5 (1H,m); 4.55
29	(1H, broad s, exchanges with D_2O); 6.95 - 7.50 (4H,
30	complex)

0 l 0 2	Preparation 41
0 3	
04	2-[N-Isopropyl-N-(2-benzoxazolyl)amino]ethanol
05	methanesulphonyl ester.
06	
07	
8 0	\sim N
09	O N O SCH 3
10	O SCH
11	33
12	
13	
14	The title compound was prepared from 2-[N-isopropyl
15	-N-(2-benzoxazolyl)amino]ethanol and methanesulphonyl
16	chloride by a similar procedure to that described in
17	Preparation 38.
18	
19	1H NMR & (CDC13)
20	
21	1.35 (6H,d); 3.0 (3H,s); 3.8 (2H,t); 4.3-4.7 (3H,
22	complex); 6.9-7.5 (4H, complex).
23	

01 02	- 59 - Example 1
03	
04	5-(4-[2-(N-Methyl-N-(2-benzothiazolyl)amino)ethoxy]benz
05	yl)-2,4-thiazolidinedione.
06	
07	
08	
o 9	CH ₃
10	S NH
11	
12	· · · · · · · · · · · · · · · · · · ·
13	
14	5-(4-[2-(N-Methyl-N-(2-benzothiazolyl)amino)ethoxy]
15	benzylidene)-2,4-thiazolidinedione (2g) in dry
16	1,4-dioxan (70ml) was reduced under hydrogen in the
17	presence of 10% palladium on charcoal (3g) at ambient
18	temperature and atmospheric pressure until hydrogen
19	uptake ceased. The solution was filtered through
20	diatomaceous earth, the filter pad was washed
21	exhaustively with dioxan and the combined filtrates
2 2	were evaporated to dryness under vacuum. The title
23	compound (m.p. 167-8°C) was obtained after
24	crystallisation from methanol.
25	
26	1H NMR δ (DMSO-d ₆)
2 7	
28	2.9-3.4 (2H, complex); 3.25 (3H, s); 3.9 (2H, complex);

4.25 (2H, complex); 4.8 (1H, complex); 6.8-7.75 (8H,

complex); 12.0 (1H, s, exchanges with D_2O).

29

30

01 02	- 60 - Example 2
03	Example 5
04	5-(4-[2-(N-Methyl-N-(2-benzothiazolyl)amino)ethoxy]
05	benzylidene)-2,4-thiazolidinedione.
06	
07	O
08	N CH A
09	NH NH
10	s s
11	
12	
13	A solution of $4-[2-(N-methyl-N-(2-benzothiazolyl)amino)]$
14	ethoxy]benzaldehyde (1.9g) and 2,4-thiazolidinedione
15	(0.8g) in toluene (100ml) containing a catalytic
16	quantity of piperidinium acetate was boiled under
17	reflux in a Dean and Stark apparatus for 2 hours. The
18	mixture was cooled and filtered and the filtered solid
19	was dried to give the title compound (mp 219°C).
20	

3.2 (3H, s); 3.9 (2H, t); 4.35 (2H, t);

 $\frac{1}{1}$ H NMR & (DMSO - $\frac{1}{1}$ A)

6.8 - 7.7 (10H, complex).

0.1 - 61 -Example 3 5-(4-[2-(N-Methyl-N-(2-benzoxazolyl)amino)ethoxy] benzyl)-2,4-thiazolidinedione hemihydrate 5-(4-[2-(N-Methyl-N-(2-benzoxazolyl)amino)ethoxy]-benzylidene)-2,4-thiazolidinedione (1.5g) in dry 1,4-dioxan (80 ml) was reduced under hydrogen in the presence of 10% palladium on charcoal (2g) at ambient temperature and atmospheric pressure until hydrogen uptake ceased. The solution was filtered through diatomaceous earth, the filter pad was washed exhaustively with dioxan and the combined filtrates were evaporated to dryness under vacuum. The title compound (mp 147 - 9° C) was obtained after crystallisation from methanol.

¹H NMR δ (DMSO-d₆+D₂0)

3

3.1-3.5 (2H, complex); 3.3 (3H,s); 3.95 (2H, complex); 4.25 (2H, complex); 4.5 (1H, complex); 6.8-7.3 (8H, complex).

. h H o

02 <u>Example 4</u>

5-(4-[2-(N-Methyl-N-(2-benzoxazolyl)amino)ethoxylbenzylidene)-2,4-thiazolidinedione

- 62 -

A solution of 4-[2-(N-methyl-N-(2-benzoxazolyl)amino)] ethoxy]benzaldehyde (1.6g) and 2,4-thiazolidinedione (0.63g) in toluene (100ml) containing a catalytic quantity of piperidinium acetate was boiled under reflux in a Dean and Stark apparatus for 2 hours. The mixture was cooled and filtered to give the title compound (mp 227 - 9° C).

1H NMR δ (DMSO-d6)

3.20 (3H, s); 3.90 (2H, t); 4.30 (2H, t); 6.9 - 7.75 (10H, complex).

01 02	- 63 - Example 5
03	<u>5,1,4</u>
04	5-(4-[2-(N-Methyl-N-(2-pyrimidinyl)amino)ethoxy]
05	benzyl)-2,4-thiazolidinedione
06	soldy 17 27 to child 2011 difficultione
07	
08	
09	0 //
10	CH ₃
11	NH S /
12	\sim \sim \sim \sim \sim
13	
14	
15	
16	5-(4-[2-(N-Methyl-N-(2-pyrimidinyl)amino)
17	ethoxy]benzylidene)-2,4-thiazolidinedione (2.4g) in dry
18	1,4-dioxan (150ml) was reduced under hydrogen in the
19	presence of 10% palladium on charcoal (3g) until
20	hydrogen uptake ceased. The solution was filtered
21	through diatomaceous earth, the filter pad was washed
22	exhaustively with dioxan and the combined filtrates
23	were evaporated to dryness under vacuum. The title
24	compound (mp 150-51°C) was obtained after
25	crystallisation from methanol.
26	w .
27	1H NMR & (DMSO-d ₆)
28	
29	2.9-3.4 (2H, complex); 3.2 (3H, s); 3.9 (2H, complex);
30	4.2 (2H, complex); 4.9 (1H, complex); 6.6 (1H, t); 6.9
31	(2H, d); 7.2 (2H, d); 8.4 (2H, d); 12.0 (1H, broad s,
32	exchanges with D ₂ O).

Example 6 5-(4-[2-(N-Methyl-N-(2-pyrimidinyl)amino)ethoxy] benzylidene)-2,4-thiazolidinedione

> A solution of 4-[2-(N-methyl-N-(2-pyrimidinyl)amino) ethoxy]benzaldehyde (1.7g) and 2,4-thiazolidinedione (0.7g) in toluene (100ml) containing a catalytic quantity of piperidinium acetate was boiled under reflux in a Dean and Stark apparatus for 2 hours. The mixture was cooled and filtered to give the title compound (mp $189 - 90^{\circ}C$).

$\frac{1}{1}$ H NMR & (DMSO-d₆ + D₂O)

3.2 (3H, s); 3.7-4.4 (4H, complex); 6.6 (1H, t); 7.1 (2H, d), 7.5 (2H, d); 7.7 (1H, s); 8.4 (2H, d).

)1)2	- 65 - Example 7
) 3	Example /
)4	5 /4 /2 /N Mothul N /2 /4 5 34-45 344 3 3 3 3 3 3
)5	5-(4-(2-(N-Methyl-N-[2-(4,5-dimethylthiazolyl)]amino)
	ethoxy benzyl)-2,4-thiazolidinedione
)6	
)7	O
38	CH ₃ N CH ₃
)9	NH NH
10	Su s
11	3
12	
13	
14	5-(4-[2-(N-Methyl-N-[2-(4,5-dimethylthiazolyl)]amino)
15	ethoxy]benzylidene-2,4-thiazolidinedione (1.6g) was
16	dissolved in a mixture of methanol (50ml) and dioxan
17	(50ml). Magnesium turnings (1.5g) were added and the
18	solution stirred until no more effervescence was
19	observed. The mixture was added to water (300ml),
20	acidified (2M HCl) to form a solution, neutralised
21	(saturated NaHCO3 solution), filtered and dried. The
2 2	solid was dissolved in dioxan (100ml), adsorbed onto
23	silica (20g) and the title compound (m.p. 177°C; MeOH)
24	obtained following chromatography on silica-gel in 5%
25	dioxan in dichloromethane.
26	
27	1H NMR & (DMSO-d6)
28	
29	2.05 (3H, s); 2.15 (3H, s); 3.0 (3H, s); 3.0-3.4 (2H,
30	complex); 3.8 (2H, t); 4.2 (2H, t); 4.85 (1H, complex);
31	6.9 (2H, d); 7.1 (2H, d); 12.0 (1H, broad s exchanges

with D_2O).

01 02	- 66 - Example 8
03	<u></u>
04	5-/4-[2-/N Mothy] N (2 // 5]:
05	5-(4-[2-(N-Methyl-N-[2-(4,5-dimethylthiazolyl)]amino)
	ethoxy benzylidene)-2,4-thiazolidinedione
06	
07	
08	
09	O
10	CH ₃ N CH ₃
11	CH 3 NH NH
12	s s
13	cH^3
14	
15	
16	
17	The title compound (m.p. 175°C) was prepared by a
18	similar procedure to that described in Example 4.
19	
20	1H NMR δ (DMSO-d ₆)
21	
2 2	2.0 (3H, s); 2.1 (3H, s); 3.0 (3H, s); 3.7 (2H, t);
2 3	4.25 (2H, t); 7.1 (2H, d); 7.55 (2H, d); 7.75 (1H, s);
24	12 0 (1H broad a cushanan will a co
25	12.0 (1H, broad s, exchanges with D_2O).

01	
02	- 67 - Example 9
03	
04	5-(4-[2-(N-Methyl-N-(2-thiazolyl)amino)ethoxy]benzyl)
05	-2,4-thiazolidinedione
06	
07	
08	
09	
10	CH ₃
11	NH NH
12	73,
13	•
14	
15	
16	
17	The title compound (m.p. 186°C; MeOH) was prepared by
18	an analogous procedure to that described in Example 7.
19	
20	1H NMR δ (DMSO-d ₆)
21	
2 2	3.0-3.4 (2H, complex); 3.1 (3H, s); 3.8 (2H, t);
2 3	4.2 (2H, t); 4.85 (1H, complex); 6.7-7.3 (6H, complex);
24	12.0 (1H, broad s, exchanges with D20).
. =	

01 02	- 68 - Example 10
03	
04	5-(4-[2-(N-Methyl-N-(2-thiazolyl)amino)ethoxy]
05	benzylidene)-2,4-thiazolidinedione
06	
07	
8 0	
09	
10	
11	NH NH
12	s n
13	70
14	
15	
16	
17	
18	The title compound (m.p. 212°C) was prepared by a
19	similar procedure to that described in Example 4.
20	•
21	1H NMR & (DMSO-d6)
22	
23	3.1 (3H, s); 3.85 (2H, t); 4.3(2H, t); 6.75 (1H, d);
24	7.1-7.3 (3H, complex); 7.6 (2H, d); 7.75 (1H, s);
2 5	12.0 (1H, broad s, exchanges with D_2O).

01	- 69 -
02	Example 11
03	
04	5-[4-(2-(N-Methyl-N-(2-(4-phenylthiazolyl))amino)]
05	ethoxy)benzyl]-2,4-thiazolidinedione
06	
07	
08	
09	
10	
11	N CH 3 NH
12	5
13	(,)
14	
15	
16	
17	
18	
19	The title compound was obtained as a foam (m.p.
20	62-65 ^o C) from 5-[4-(2-(N-methyl-N-
21	(2-(4-phenylthiazolyl))amino)ethoxy)benzylidene]
2 2	-2,4-thiazolidinedione (1.6g) by a similar procedure to
23	that described in Example 7.
24	
25	1H NMR δ (DMSO-d6)
26	
27	3.15 (3H, s); 3.0-3.4 (2H, complex); 3.9 (2H, t);
28	4.25 (2H, t); 4.85 (1H complex); 6.9 (2H, d); 7.1-7.45
29	(6H, complex); 7.85 (2H, d); 12.0 (1H, broad s,
30	exchanges with D ₂ O).

01	22
5 2	- 70 - Example 12
3 3	
34	5-(4-[2-(N-Methyl-N-(2-(4-phenylthiazolyl))amino)]
35	ethoxy benzylidene)-2,4-thiazolidinedione
76	
7 7	
38	
9	N CH ₃
10	NH NH
11	
12	\ `0
13	
14	
15	
16	The title compound (m.p. 134°C) was prepared from
17 .	4-[2-(N-methyl-N-(2-(4-phenylthiazolyl))amino)ethoxy]
18	benzaldehyde by a similar procedure to that described
19	in Example 4.
20	
21	1H NMR & (DMSO-d6)
2 2	
23	3.2 (3H, s); 3.9 (2H, t); 4.35 (2H, t); 7.1-7.95
24	(11H, complex); 12.0 (1H broad s, exchanges with D_2O).

01 02	- 71 -
03	Example 13
04	5-(4-[2-(N-Methyl-N-[2-(4-phenyl-5-methylthiazolyl)]
05	amino)ethoxy benzyl)-2,4-thiazolidinedione
06	
07	
08	
09	
10	N CH ₃
11	NH NH
12	
13	CH ³
14	
15	
16	
17	
18	The title compound, obtained as a foam
19	(m.p. 60-62 ^O C), was prepared by an analogous procedure
20	to that described in Example 7.
21	
22	1H NMR δ (DMSO-d6)
23	
24	2.35 (3H, s); 3.1 (3H, s); 3.0-3.4 (2H, complex);
25	3.8 (2H, t); 4.2 (2H, t); 4.85 (1H, complex);
	<u> </u>

6.9 (2H, d); 7.2 (2H, d); 7.25-7.5 (3H, complex);

7.65 (2H, d); 12.0 (1H, broad s, exchanges with D_2O).

01 02
03
04
0 5
06
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2**5** 2**6**

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Example 14

- 72 -

5-(4-[2-(N-Methyl-N-[2-(4-phenyl-5-methylthiazolyl)] amino)ethoxy]benzylidene)-2,4-thiazolidinedione

The title compound was prepared from 4-[2-(N-methyl-N-[2-(4-phenyl-5-methylthiazolyl)]amino)ethoxy] benzaldehyde by a similar procedure to that described in Example 4, and was used in Example 13 without further purification.

1H NMR & (DMSO-d6)

2.4 (3H, s); 3.1 (3H, s); 3.8 (2H, t); 4.35 (2H, t); 7.1-7.75 (10H, complex); 12.0 (1H, broad s, exchanges with D_2O).

73 -

Example 15

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 $\frac{5-(4-[2-(N-Methyl-N-[2-(4-methyl-5-phenylthiazolyl)]}{amino)ethoxy[benzyl)-2,4-thiazolidinedione}$

The title compound (m.p. 174° C; MeOH) was prepared from 5-(4-[2-(N-methyl-N-[2-(4-methyl-5-phenylthiazolyl)]-amino)ethoxy]benzylidene)2,4-thiazolidinedione by an analogous procedure to that described in Example 7.

1H NMR δ (DMSO-d6)

2.3 (3H, s); 3.0-3.4 (2H, complex); 3.15 (3H, s); 3.85 (2H, t); 4.25 (2H, t); 4.85 (1H, complex); 6.95 (2H, d); 7.2 (2H, d); 7.45 (5H, complex); 12.0 (1H, broad s, exchanges with D₂O).

01 02	- 74 - Example 16
03	
04	5-(4-[2-(N-Methyl-N-[2-(4-methyl-5-phenylthiazolyl)]
05	amino)ethoxy benzylidene)-2,4-thiazolidinedione
06	
07	
08	
0 9	O
10	CH ₃ CH ₃
11	NH NH
12	s
13	\(\begin{array}{c} \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\
14	
15	
16	
17	
18	The title compound was prepared from
19	4-[2-(N-methyl-N-[2-(4-methyl-5-phenylthiazolyl)]
20	amino)ethoxy]benzaldehyde by a similar procedure to
21	that described in Example 4, and was used in Example 15
2 2	without further purification.
2 3	
24	1H NMR & (DMSO-d6)
25	
2 6	2.3 (3H, s); 3.1 (3H, s); 3.85 (2H, t); 4.35 (2H, t);
27	7.15-7.75 (10H, complex); 12.0 (1H, broad s, exchanges
28	with D ₂ O).

29

01 02	- 75 - <u>Example</u> 17
03	
04	5-(4-[2-(N-Methyl-N-[2-(4-methylthiazolyl)]
05	amino)ethoxy benzyl)-2,4-thiazolidinedione
06	
07	
08	
09	0
10	
11	CH ₃ NH NH
12	s
13	ò
14	
15	
16	
17	
18	
19	The title compound, was prepared from 5-(4-[2-(N-methyl
20	-N-[2-(4-methylthiazolyl)]amino)ethoxy]benzylidene)-
21	$2,4$ -thiazolidinedione as a foam (m.p. 121° C), by a
22	similar procedure to that described in Example 7.
23	
24	1H NMR & (DMSO-d6)
2 5	
26	2.1 (3H, s); 3.0-3.4 (2H, complex); 3.1 (3H, s);
27	3.75 (2H, t); 4.15 (2H, t); 4.85 (1H, complex);
28	6.3 (1H, s); 6.9 (2H, d); 7.2 (2H, d);
29	12.0 (1H, broad s, exchanges with D2O).

- 76 -

Example 18

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5-(4-[2-(N-Methyl-N-[2-(4-methylthiazolyl)]amino) ethoxy]benzylidene)-2,4-thiazolidinedione

The title compound was prepared from 5-(4-[2-(N-methyl-N-[2-(4-methylthiazolyl)] amino)ethoxy]benzaldehyde by a similar procedure to that described in Example 4, and was used in the Example 17 without further purification.

1H NMR δ (DMSO-d6)

2.1 (3H, s); 3.1 (3H, s); 3.85 (2H, d); 4.3 (2H, d); 6.3 (1H, s); 7.15 (2H, d); 7.6 (2H, d); 7.75 (1H, s); 12.0 (1H, broad s, exchanges with D₂O).

01 02	- 77 - Example 19
03	Example 19
04	5-[4-(2-(N-Mothy) N (2 (5 phon))
05	5-[4-(2-(N-Methyl-N-[2-(5-phenyloxazolyl)]amino)
26	ethoxy)benzyl]-2,4-thiazolidinedione
27	
08	
39	O
10	CH ₃
11	NH
12	s
13	
14	
15	
16	
17	
18	The title compound (m.p. 200°C, MeOH)) was prepared
19	from 5-[4-(2-(N-methyl-N-[2-(5-phenyloxazolyl)]amino
20	ethoxy)benzylidene]-2,4-thiazolidinedione by a similar
21	procedure to that described in Example 7.
2 2	
2 3	1H NMR δ (DMSO-d6)
24	
25	3.0-3.4 (2H, complex); 3.15 (3H, s); 3.8 (2H, t);
26	4.2 (2H, t); 4.85 (1H, complex); 6.9 (2H, d);

7.1-7.4 (6H, complex); 7.5 (2H, d);

12.0 (1H, broad s, exchanges with D_2O).

27

01 02	- 78 - Example 20
03	Example 20
04 .	5-(4-(2-(N-Methy) N (2 /5 phony) cycrolul) 2-(-1-1-1)
05	5-(4-[2-(N-Methyl-N-[2-(5-phenyloxazolyl)]amino)
06	ethoxy benzylidene)-2,4-thiazolidinedione
07	
08	O
	\wedge \wedge \vee
09	CH 3 NH
10	s s
11	
12	
13	
14	
15	
16	The title compound (m.p. 191°C) was prepared from
17	4-[2-(N-methyl-N-[2-(5-phenyloxazolyl)]amino)
18	ethoxy]benzaldehyde by an analogous procedure to that
19	described in Example 4.
20	•
21	1H NMR δ (DMSO-d ₆)
2 2	
23	3.2 (3H, s); 3.8 (2H, t); 4.35 (2H, t); 7.1-7.7
24	10H, complex); 7.8 (1H, s); 12.0 (1H, broad s,
25	exchanges with D ₂ O).
26	
27	Example 21
28	
29	5-(4-[2-(N-Methyl-N-[2-(4,5-dimethyloxazolyl)]amino)
30	ethoxy benzyl)-2,4-thiazolidinedione
31	o
32	
33	CH ₃ NH
34	l
35	CH ₃
36	J

5-(4-[2-(N-Methyl-N-[2-(4,5-dimethyloxazolyl)]amino)-

- 79 ethoxy]benzylidene)-2,4-thiazolidinedione (1.2g) in dry 1,4-dioxan (100ml) was reduced under hydrogen in the presence of 10% Palladium on charcoal (2.5g) until hydrogen uptake ceased. The solution was filtered through diatomaceous earth, the filter pad was washed exhaustively with dioxan and the combined filtrates evaporated to dryness under vacuum. The title compound was obtained as a foam (m.p. 53-54°C) following chromatography on silica-gel in 1% methanol in dichloromethane. $\frac{1}{1}$ H NMR & (DMSO- $\frac{1}{1}$ 6) 1.85 (3H, s); 2.05 (3H, s); 3.0 (3H, s); 3.0-3.4 (2H, complex); 3.65 (2H, t); 4.1 (2H, t); 4.85 (1H, complex); 6.85 (2H, d); 7.15 (2H, d); 12.0 (1H, broad s, exchanges with D20). Example 22 5-(4-[2-(N-Methyl-N-[2-(4,5-dimethyloxazolyl)]amino)ethoxy|benzylidene)-2,4-thiazolidinedione

 The title compound (softens at 149°C) was prepared by a

similar procedure to that described in Example 4.

01 02	- 80 - 1H NMR δ (DMSO-d ₆)
03	
04	1.85 (3H, s); 2.05 (3H, s); 3.0 (3H, s); 3.7 (2H, t);
05	4.25 (2H, t); 7.1 (2H, d); 7.5 (2H, d); 7.75 (1H, s);
06	12.0 (1H, broad s, exchanges with D_2O).
07	
08	EXAMPLE 23
0 9	

thiazolidinedione

N H O S O

5-[4-(2-(2-Pyrimidinylamino)ethoxy)benzyl]-2,4-

A mixture of 5-[4-(2-(2-pyrimidinylamino)ethoxy) benzylidene]-2,4-thiazolidinedione (3g) and 10% palladium on charcoal (9g) in DMF (70ml) was stirred under a pressure of 200 psi of hydrogen until hydrogen uptake ceased. The mixture was filtered through diatomaceous earth, and the filter pad washed exhaustively with DMF. The combined filtrates were evaporated to dryness and the title compound (m.p. 173°C) obtained following recrystallization from methanol.

1H NMR & (DMSO-d6)

3.0 -3.4 (2H, complex); 3.65 (2H, complex); 4.1 (2H,

01 02	- 81 -
03	t); 4.85 (1H, complex); 6.6 (1H, t); 6.85 (2H, d);
04	7.15 (2H, d); 7.25 (1H, t, exchanges with D ₂ O);
05	8.3 (2H, d); 12.0 (1H, broad s, exchanges with D_2O).
06	EVANDED 24
	EXAMPLE 24
07	
08	5-[4-(2-(2-Pyrimidinylamino)ethoxy)benzylidene]-2,4-
09	thiazolidinedione
10	
11	
12	
13	
14	H
15	N N N NH
16	
17	
18	
19	
20	
21	
22	The title compound (m.p. 234°C) was obtained from
23	4-[2-(2-pyrimidinylamino)ethoxy]benzaldehyde and 2,4-
24	thiazolidindione, by an analogous procedure to that
25	described in Example 6.
26	
27	1H NMR δ (DMSO-d ₆)
28	
29	3.65 (2H, complex); 4.2 (2H,t); 6.6 (1H, t); 7.0-7.6
30	(5H, complex, one proton changes with D_2O); 7.7 (1H,
31	s); 8.3 (2H, d); 12.0 (1H, broad s, exchanges with

 D₂O).

02 <u>EXAMPLE 25</u>

5-(4-[2-(N-Acetyl-N-(2-pyrimidinyl)amino)ethoxy]benzyl)
-2,4-thiazolidinedione

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A stirred solution of 5-[4-(2-(2-pyrimidinylamino) ethoxy)benzyl]-2,4-thiazolidinedione (800mg) in acetic anhydride (15ml) and 1,4-dioxan (5ml) was boiled under reflux for 3 hours. After cooling, the mixture was added to water (300ml), neutralized (sodium bicarbonate) and extracted with dichloromethane (3x200ml). The organic extracts were washed with brine (100ml), dried (MgSO₄), filtered and evaporated to dryness. Chromatography on silica-gel in dichloromethane of the residual oil afforded the title compound (m.p. 137°C).

1H NMR & (DMSO-d6)

- 2.3 (3H, s); 2.93.4 (2H, complex); 4.15 (2H,t);
- 4.35 (2H, t); 4.85 (1H, complex); 6.7 (2H,d);
 - 7.1 (2H, d); 7.35 (1H, t); 8.8 (2H, d);
- 12.0 (1H, broad s, exchanges with D_2O).

)1)2	- 83 - EXAMPLE 26
23	<u> </u>
04	5-(4-(2-(N-(2-Benzothiazolyl)-N-benzylamino)ethoxy)
)5	benzylidene)-2,4-thiazolidinedione
06	<u>maj = = onaj = j = onid = olidined i olie</u>
37	
28	
) 9	
10	
11	NH NH
12	s s
L 3	,0
14	
15	
16	4-(2-(N-(2-Benzothiazolyl)-N-benzylamino)ethoxy)
L 7	benzaldehyde (3g) and 2,4-thiazolidinedione (1g) were
18	dissolved in toluene (200ml) containing piperidine
19	(0.2ml) and benzoic acid (0.2g) and heated to reflux
20	for 4h. in a Dean and Stark apparatus. On cooling, the
21	solution was concentrated under vacuum to 50% of its
2 2	volume and the title compound, which crystallised, was
23	collected by filtration and dried <u>in vacuo</u> (m.p.
24	185-188 ^O C). It was used in Example 27 without further
25	purification.
2 6	
27	1H NMR & (DMSO-d ₆)

4.0 (2H, t); 4.4 (2H, t); 4.9 (2H, s); 7.1-7.9 (14H,

complex); 12-13 (1H, broad s, exchanges with D_2O).

EXAMPLE 27

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5-(4-(2-(N-(2-Benzothiazolyl)-N-benzylamino)ethoxy)benzyl)-2,4-thiazolidinedione

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5-(4-(2-(N-(2-Benzothiazolyl)-N-benzylamino)ethoxy) benzylidene)-2,4-thiazolidinedione (2.4g) in dioxan (150ml) was hydrogenated in the presence of 10% palladium-charcoal (4.8g) for 3h. at room temperature and atmospheric pressure. A further portion of catalyst (2.4g) was added and the hydrogenation continued for a total of 20h. The mixture was filtered through diatomaceous earth and the solvent was evaporated. The residue was chromatographed on silica gel with 3% methanol-dichloromethane as eluant to afford the title compound as a foam, which collapsed at 78°C.

1H NMR & (CDCl3)

- 3.1 (1H, dd); 3.4 (1H, dd); 4.0 (2H, t); 4.25 (2H, t);
- 4.5 (1H, dd); 4.9 (2H, s); 6.8-7.6 (13H, m);
- 8.3 (1H, broad s, exchanges with D_2O).

)1	- 85 -
72	EXAMPLE 28
O 3	
04	5-(4-[3-(N-Methyl-N-(2-benzoxazolyl)amino)propoxy]
05	benzyl)-2,4-thiazolidinedione
06	
07	O //
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၁ 9	N CH ₃
10	\sim
11	0
12	
13	
14	The title compound (m.p. 171-3°C; ethanol) was prepared
15	from $5-(4-[3-(N-methyl-N-(2-benzoxazolyl)amino)-$
16	propoxy]benzylidene)-2-4-thiazolidinedione by a similar
17	procedure to that described in Example 1.
18	
19	$\frac{1}{1}$ H NMR & (DMSO - $\frac{1}{1}$ 6)
20	

with D_2O).

21

2**2**

? **3**

24 25 2.0-2.35 (2H, complex); 2.9-3.6 (2H, complex); 3.2 (3H,

6.8-7.4 (8H, complex); 12-12.5 (1H, broad s, exchanges

s); 3.7 (2H, t); 4.2 (2H, t); 4.9 (1H, complex);

EXAMPLE 29

5-(4-[3-(N-Methyl-N-(2-benzoxazolyl)amino)propoxy]-benzylidene)-2,4-thiazolidinedione

$$\begin{array}{c|c} & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & &$$

The title compound (m.p. $202-204^{\circ}$ C) was prepared from 4-[3-(N-methyl-N-(2-benzoxazolyl)amino)propoxy]benzaldehyde (5.3g) and 2,4-thiazolidinedione (2.2g) by a similar procedure to that described in Example 4.

$\frac{1}{1}$ H NMR & (DMSO - d₆)

2.0-2.35 (2H, complex); 3.15 (3H, s); 3.7 (2H, t); 4.2 (2H, t); 7.0-7.7 (8H, complex); 7.8 (1H, s); 12.0 (1H, broad s, exchanges with D₂O).

EXAMPLE 30

5-(4-[2-(N-Methyl-N-(2-pyridyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione

01 02	The title compound (T. a.
03	The title compound (m.p. 153-5°C; MeOH) was obtained
04	from 5-(4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]-
05	benzylidene)-2,4-thiazolidinedione by a similar
06	procedure to that described in Example 1.
07	It was a cover a cover as
08	$\frac{1}{1}$ H NMR & (DMSO - d ₆)
09	
	2.9-3.4 (2H, complex); 3.1 (3H, s); 3.9 (2H, t); 4.15
10	(2H, t); 4.8 (1H, complex); 6.5-6.85 (2H, complex); 6.8
11	(2H, d); 7.2 (2H, d); 7.5 (1H, complex); 8.1 (1H, d);
12	12.05 (1H, broad s, exchanges with D_2O).
13	
14	EXAMPLE 31
15	
16	5-(4-[2-(N-Methyl-N-(2-pyridyl)amino)ethoxy]benzyl-
17	<u>idene)-2,4-thiazolidinedione</u>
18	
19	o
20	CH CH
21	Ch 3 NH
2 2	's 's
2 3	0
24	
25	The title compound (m.p. 177-9°C) was obtained from
26	4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzaldehyde
27	(3.2g) and 2,4-thiazolidinedione (1.1g) by a similar
28	procedure to that described in Example 4.
29	•
30	1H NMR δ (DMSO-D2O)
31	
32	3.1 (3H, s); 3.9 (2H, t); 4.2 (2H, t); 6.4-7.5 (7H,
22	gomplous 7 7 (1) - 1 0 1 1 1 2

complex); 7.7 (1H, s); 8.1 (1H, d)

D2 <u>Example 32</u>

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01

5-(4-[4-(N-Methyl-N-(2-benzoxazolyl)amino)butoxy] benzylidene)-2,4-thiazolidinedione.

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6 7 CH₃
NH

The title compound (m.p. 168° C) was prepared from 4-[4-(N-methyl-N-(2-benzoxazolyl)amino)butoxy]benzal dehyde (3.5g) and 2,4-thiazolidinedione (1.4g) by a similar procedure to that described in Example 4.

1H NMR δ DMSO-d6

1.70 (4H, complex); 3.10 (3H, s); 3.25 (1H, exchanges with D_2O); 3.50 (2H, complex); 4.05 (2H, complex); 6.90-7.60 (8H, complex); 7.70 (1H, s).

Example 33

5-(4-[4-(N-Methyl-N-(2-benzoxazolyl)amino)butoxy]-benzyl)-2,4-thiazolidinedione

The title compound (m.p. 112°C, ethanol-hexane) was

)1)2	- 89 -
) 3	prepared from 5-(4-[4-(N-methyl-N-(2-benzoxazolyl)-
04	amino)butoxy]benzylidene)-2,4-thiazolidinedione by a
25	similar procedure to that described in Example 1.
)6	¹ Η NMR δ CDCl ₃
	TH NMR 6 CDC13
)7	1 05 (4)
28	1.85 (4H, complex); 3.10 (1H, complex); 3.15 (3H,s);
)9	3.40 (1H,dd); 3.60 (2H,t); 4.00 (2H,t); 4.50 (1H,dd);
10	6.80-7.40 (8H, complex); 9.30 (1H, br, exchanges with
11	D ₂ O).
12	
L 3	Example 34
L 4	
15	5-(4-[2-(N-(2-Benzoxazolyl)amino)ethoxy]benzylidene)-
16	2,4-thiazolidinedione
1.7	
18	
19	Q
20	
21	ЙН
2 2	NH O S
2 3	~ •
24	
25	
26	"
27	The title compound (m.p. 242-5°C) was prepared from
28	4-[2-(N-(2-benzoxazolyl)amino)ethoxy]benzaldehyde
29	(5.18g) and 2,4-thiazolidinedione (2.36g) by a similar
30	procedure to that described in Example 4.
31	•
32	1H NMR & DMSO-d6
3 3	
3 4	3.80 (2H,t); 4.35 (2H,t); 7.00-8.00 (9H, complex); 8.20
} 5	(1H, br, exchanges with D ₂ O); 13.5 (1H, br, exchanges

with D_2O).

01 02	- 90 - Example 35
03	
04	5-(4-[2-(N-(2-Benzoxazolyl)amino)ethoxy]benzyl)-2,
05	4-thiazolidinedione
06	
07	
08	
09	
10	NH S NH
11	
12	
13	
14 .	
15	The title compound (m.p. 202-3°C; dichloromethane) was
16	prepared from 5-(4-[2-(N-(2-benzoxazolyl)amino)ethoxy]
17	benzylidene)-2,4-thiazolidinedione (6.1g) by a similar
18	procedure to that described in Example 1.
19	
20	1H NMR & DMSO-d6
21	
2 2	3.10 (1H,dd); 3.30 (1H,dd) 3.70 (2H, complex); 4.15
23	(2H,t); 4.85 (1H,dd); 6.80-7.50 (8H, complex); 8.15

exchanges with D_2O).

2**4** 2**5**

26

(1H, complex; exchanges with D_2O); 12.00 (1H, br,

- 91 -

21 2 (Example 36

3

14 5-(4-[2-(N-Isopropyl-N-(2-benzoxazolyl)amino)ethoxy] benzyl)-2,4-thiazolidinedione. 25

brine (11), dried (MgSO₄) and evaporated.

compound as a foam (m.p. 66°C).

1H NMR & (CDCl₃)

D₂O).

oil was chromatographed on silica gel with 1.5%

methanol-dichloromethane as solvent to afford the title

1.35 (6H,d); 3.1 (1H, dd); 3.4 (1H, dd); 3.8 (2H,t);

4.15 (2H, complex); 4.35-4.65 (2H, complex); 6.85-7.4

(8H, complex); and 9.15 (1H, broad s,; exchanges with

The residual

26

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13

Sodium hydride (60% dispersion in mineral oil, 0.93q) was added portionwise to a stirred solution of 5-15 16 (4-hydroxybenzyl)-2,4-thiazolidinedione (2.45g in dry 17 DMF (50ml)) at room temperature under a nitrogen 18 atmosphere. The mixture was stirred for 1 hour prior to the addition of a solution of 19 20 2-[N-isopropyl-N-(2-benzoxazolyl)amino]ethanol 21 methanesulphonyl ester (3.3q) in dry DMF (60ml). stirring at room temperature for a further hour, the

mixture was heated at 80°C for 21 hours, then cooled, 23 diluted with water (11) and acidified to pH 6.5 with 2**5** hydrochloric acid. The resulting suspension was extracted with ethyl acetate (2x500ml), and the combined ethyl acetate layers washed with water (3x11),

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DEMONSTRATION OF EFFICACY OF COMPOUNDS

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Obese Mice, Oral Glucose Tolerance Test.

C57bl/6 obese (ob/ob) mice were fed on powdered oxoid diet. After at least one week, the mice continued on a powdered oxoid diet or were fed powdered oxoid diet containing the test compound. After 8 days on the supplemented diet all of the mice were fasted for 5 hours prior to receiving an oral load of glucose (3 g/kg). Blood samples for glucose analysis were taken 0, 45, 90 and 135 minutes after glucose administration and the results appear below as the percentage reduction in area under the blood glucose curve where test compound treated groups are compared with the control groups. 7 mice were used for each treatment.

EXAMPLE NO:	LEVEL IN DIET (µmol kg ⁻¹ of DIET)	%REDUCTION IN AREA UNDER BLOOD GLUCOSE CURVE
	•	CORVE
1	100	51
2	300	30
3	10	39
4	300	30
5	100	40
7	50	47
9	100	58
11	100	34
13	100	37
15	100	39
17 .	100	34
19	30	22
21	30	33
24	30	15
25	30	19
27	300	56
29	300	32
33	300	25
35	100	44
36	100	20
	100	40

- 93 -

01 02

Anti-Hypertensive Activity

03 • 04

05

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07

80 09 Eight month old female, spontaneously hypertensive rats were given test compound once each day for 15 days. Prior to the experiment and on days 8 and 15, the rats were fasted overnight from 5.00 pm and blood pressure was recorded the following morning, immediately prior to dosing and again 2h later. Food was returned after the 2h blood pressure reading.

11 12 13

10

The results below were obtained using the compound of Example 3 as the test compound.

14 15 16

17			Blood pres	sure(mm Hg)
18	Treatment Group	Time	O hours	2 hours
19				
20				
21	Control	Day 0	210 ± 13	-
22	Test Compound (30µmole/kg)	Day 0	210 ± 13	-
23	Test Compound (10µmole/kg)	Day 0	210 ± 13	-
24				
25	Control	Day 8	196 ± 11	195 ± 12
26	Test Compound (30µmole/kg)	Day 8	181 ± 11*	174 ± 15**
27	Test Compound (10µmole/kg)	Day 8	191 ± 6	185 ± 12
28				
29	Control	Day 15	208 ± 12	208 ± 9
30	Test Compound (30µmole/kg)	Day 15	178 ± 18**	170 ± 13***
31	Test Compound (10µmole/kg)	Day 15	198 ± 17	185 ± 5***
32				

33 34

Significance of difference from control value at same timepoint:

36 37

^{*}p<0.05; **p<0.01; ***p<0.001.

- 94
Toxicology

No toxicological effects were indicated for any of the compounds of the invention in any of the abovementioned tests.